PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FC 858/5		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/08307	27/10/1999	30/10/1998
International Patent Classification (IPC) or national classification and IPC C07D277/48		
Applicant PHARMACIA & UPJOHN S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/05/2000	26.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fanni, S Telephone No. +49 89 2399 8712

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/08307

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-3,5,8-11, 13-70	as originally filed			
4,6,7,12	as received on	17/02/2000	with letter of	14/02/2000

Claims, No.:

7 (part),8-16	as originally filed			
1-6,7 (part)	as received on	17/02/2000	with letter of	14/02/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5, 9, 11-13
	No:	Claims	1, 2, 6-8, 10, 14-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

ITEM V

Reference is made to the following documents:

D1: FR 7 428 M
D2: DE 15 67 044 A
D3: FR-A-2 252 808
D4: DE 20 40 580 A
D5: CH 451 156 A
D6: WO 97 40028 A
D7: EP-A-0 069 784
D8: JOURNAL OF THE AMERICAN OIL CHEMISTS' SOCIETY., vol. 59, no. 10, October 1982, pages 448-452
D9: CHEM ABS, vol. 51, no. 3, 10 February 1957, abstract no. 2182d
D10: ARZNEIMITTEL FORSCHUNG. DRUG RESEARCH., vol. 37, no. 3, 1987, pages 306-309
D11: JOURNAL OF MEDICINAL CHEMISTRY., vol. 15, no. 1, 1972, pages 101-103
D12: JOURNAL OF MEDICINAL CHEMISTRY., vol. 15, no. 9, 1972, pages 955-963
D13: JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY., vol. 26, no. 1, 1978, pages 164-166,
D14: CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 21, no. 11, November 1973, pages 2408-2416
D15: JOURNAL OF THE CHEMICAL SOCIETY,1958, pages 2815-2821
D16: EP-A-0 928 790

The applicant has not explained the reason for the provisos found in claims 6 and 7.

NOVELTY (Article 33(2) PCT)

The present subject matter is novel over D1 on account of the first proviso of claim 6 and the first proviso of claim 7 which disclaim the compounds disclosed in table II of D1.

The subject matter of present claims 7-16 overlaps with the subject matter disclosed by D2, with one compound specifically disclosed by D2 (namely the N-(5-methyl-2-thiazolyl)-N'N'-dimethylurea, see D2, page 7) falling into the overlap region. Other compounds disclosed by D2 (namely the N-(5-chloro-2-thiazolyl)-N'N'-dimethylurea, N-(5-chloro-2-thiazolyl)-N'-methylurea, N-(5-methyl-2-thiazolyl)-N'-methylurea, and N-(5-methyl-2-thiazolyl)-N'-phenylurea) are disclaimed by the proviso a), b) and d) of present claim 7. Accordingly, the subject matter of present claims 7, 8, 10 and 14-16 is not novel over D2 (it is pointed out in this respect that an indication of use in a composition claim is not limitative).

The present subject matter is novel over D3 mainly on account of the proviso a) of claim 7 which disclaims the N-(5-bromo-2-thiazolyl)-N'-ethylurea and the N-(5-bromo-2-thiazolyl)-N'-methylurea disclosed on the example 1 of D3.

The present subject matter is novel over D4 mainly on account of the proviso a) of claim 7 which disclaims compounds 16-18 from D4.

D5 discloses the N-(5-nitro-2-thiazolyl)-N'-2-chlorethylurea which destroys the novelty of present claims 7, 10 and 14-16. Said compound has also a pharmaceutical application, namely as anti-parasite. Present claim 6 is therefore also not novel over D5.

The present subject matter overlaps with the subject matter of D6, with compounds 31 from table IB, page 23 of D6 being disclaimed by the provisos b) of present claims 6 and 7. Said compound has however a medical use as, among the other, anti-tumour and anti-cancer agent (see D6, page 6, lines 13-26 and claim 44 from D6), and therefore clearly destroys the novelty of present claims 2. It is also considered to anticipate claim 1 since the properties known for D6 fall within the scope of cell proliferative disorders.

The present subject matter differs from D7 mainly on account of the fact that the position 4 of the thiazole ring is unsubstituted in present compounds.

Compounds 89-93 disclosed by D8 (see D8, page 451, Table V), destroy the novelty of present claims 7, 10 and 14-16.

D9 discloses 1-alkyl and 1-aryl-3-(5-nitro-2-thiazolyl)ureas which destroy the novelty of present claims 7, 10 and 14-16. Said compounds have also a medical application, namely against enterohepatitis. Present claim 6 is therefore also not novel over D9.

Compounds Ba 30515, Ba 36435, Ba 34358, Ba 36204, Ba 32476 disclosed by D10 (see D10, page 307, Table 1), destroy the novelty of present claims 7, 10 and 14-16. Said compounds have also a pharmacological activity, namely an antitrichomonadal activity. Present claim 6 is therefore also not novel over D10.

Compounds 1-6 and 8-9 disclosed by D11 (see D11, page 307, Table 1), destroy the novelty of present claims 7, 10 and 14-16. Said compounds have also a pharmacological activity, namely an antibacterial activity. Present claim 6 is therefore also not novel over D11.

D12 discloses (5-nitro-2-thiazolyl)ureas, namely 1-ethyl-3-(5-nitro-2-thiazolyl)urea, 1-cyclohexyl-3-(5-nitro-2-thiazolyl)urea, 1-n-hexyl-3-(5-nitro-2-thiazolyl)urea, 1-tert-butyl-3-(5-nitro-2-thiazolyl)urea and 1-(3-nitro-2-thiazolyl)-3-(2-phenylcyclopropyl)urea (see D12, page 962, under: Procedure B) which destroy the novelty of present claims 7, 10 and 14-16. Said compounds have also a pharmacological activity, namely an antibacterial activity. Present claim 6 is therefore also not novel over D12.

The subject matter of present claim 7-16 is novel over D13 and D14 mainly on account of the first proviso of claim 7 which disclaims compound 5 from D13 (see D13, table I, page 165) and compound 9 from D14 (see D4, page 2409).

D15 discloses (5-nitro-2-thiazolyl)ureas, namely N'-phenyl-N-(5-nitro-2-thiazolyl)urea, N'-p-chlorophenyl-N-(5-nitro-2-thiazolyl)urea, N'-p-fluorophenyl-N-(5-nitro-2-thiazolyl)urea and N'-(3, 4-dichlorophenyl-N-(5-nitro-2-thiazolyl)urea (see D15, page 2817, under: Ureas derivatives from nitrogen heterocylcles) which destroy the novelty of present claims 7, 10 and 14-16.

Provided that the claimed priority is valid, D16 is not a relevant document for a PCT examination (see present point VI). It is however pointed out, that during the national phase, the following arguments could be relevant: the present subject matter overlaps with the subject matter disclosed by D16 (see D16, claim 1, definition of R1-R6, a and

b). The compound of formula (I) according to claim 1 from D16 have a medical application, among the other, in the prevention of tumour growth.

INVENTIVE STEP (Article 33(3) PCT)

D7 is considered to be the closest prior art and discloses thiazolylurea derivatives which are useful, among the other, for the immunotherapy of cancer. The present subject matter differs from D7 mainly on account of the fact that the position 4 of the thiazole ring is unsubstituted in present compounds, while it is occupied by a lower alkyl group or a substituted or unsubstituted phenyl residue in compounds of formula (I) according to claim 1 from D7. However, the equivalence between lower alkyl and hydrogen is disclosed by the combined teaching of D6 and D7 (see D6, page 23, compound 31). The present modifications to the parent structure of D7 are therefore considered as an obvious solution to the problem of providing further thiazolylurea anti-cancer agents.

Therefore, an inventive step cannot be acknowledged for the present subject matter.

It is also pointed out on this context, that properties establishing an inventive step should extend to the whole of the scope claimed. Generic and open-ended expressions, such as "optionally substituted" or "aryl" are certainly not suited for this purpose, since they encompass possibilities for which it would be hardly possible to show an inventive step in a representative manner.

ITEM VI

Certain published documents: EP-A-0 928 790

ITEM VII

The term "aryl" (description, page 9. line 22) as defined in the present application has a much broader meaning than that generally accepted in the art for such term, contrary to the requirements of Rule 10.1(e) PCT. For instance, the skilled person would not have considered, when reading the claims, the term aryl as encompassing heterocyclic rings.

ITEM VIII

Compounds 2 and 231 of claim 13 have been previously disclaimed in by proviso a) and b) of claim 7. This causes a lack of clarity in claim 13.

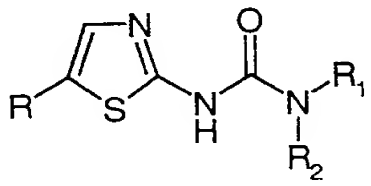
reference, US 3,726,891 in the name of Shell Co., and C.A. 83(1975):114381].

Just few examples among them are N'-methyl- and N'-ehtyl-N-(5-bromo-2-thiazolyl)-urea; N'-methyl-, N'-ethyl- or N'-phenyl-N-(5-chloro-2-thiazolyl)-urea; N-(5-chloro-2-thiazolyl)-N',N'-dimethyl-urea; N-(5-bromo-2-thiazolyl)-N',N'-dimethyl-urea; N'-methyl- and N'-phenyl-N-(5-methyl-2-thiazolyl)-urea.

Other 2-ureido-1,3-thiazole derivatives have been described in the art as therapeutic agents.

Among them are N-methyl- and N-phenyl-N'-(5-chloro-2-thiazolyl)-urea which have been described as sedative and antiinflammatory agents in FR M. 7428 (Melle-bezons) or N-[4-(5-oxazolyl)phenyl]-N'-(5-methyl-2-thiazolyl)-urea, described as inosine 5'-monophosphate dehydrogenase inhibitor (IMPDH) in WO 97/40028 (Vertex Pharmaceuticals Inc.).

Accordingly, the present invention provides the use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

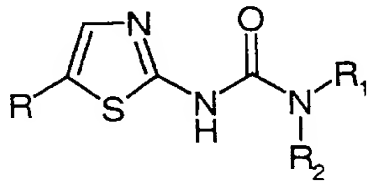
i) straight or branched C_1-C_6 alkyl;

glomerulonephritis and post-surgical stenosis and restenosis.

In addition, being useful in the treatment of cell proliferative disorders associated with an altered cell dependent kinase activity, hence cell cycle inhibition or cdk/cyclin dependent inhibition, the compounds of formula (I) of the invention also enable tumor angiogenesis and metastasis inhibition.

As above reported, some of the compounds of formula (I) of the invention have been reported in the art as useful therapeutic agents, for instance as antiinflammatory, sedative and analgesic agents.

Therefore, it is a further object of the present invention a compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

i) straight or branched C_1-C_6 alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

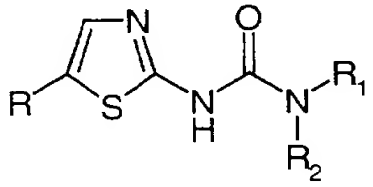
for use as a medicament; provided that:

a) when R is a chlorine atom and R_2 is hydrogen, then R_1 is not methyl, phenyl or trifluoromethylphenyl; and

b) when R is methyl and R_2 is hydrogen, then R_1 is not 4-(5-oxazolyl)phenyl.

Among the compounds of formula (I) above reported, several derivatives result to be novel.

Therefore, the present invention further provides a compound which is a 2-amino-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

iii) C_3-C_6 cycloalkyl;

iv) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

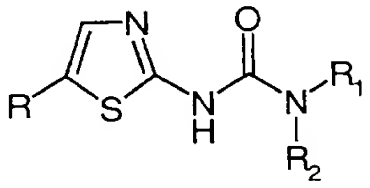
The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

Preferred compounds of the invention are the compounds of formula (I) wherein R is a halogen atom, a straight or branched C_1-C_4 alkyl group, a phenyl or a cycloalkyl group; R_2 is hydrogen and R_1 is an optionally substituted group selected from alkyl, aryl or arylakyl.

Even more preferred, within this class, are the compounds of formula (I) wherein R is bromine or chlorine, a straight or branched C_1-C_4 alkyl group, a phenyl or a cycloalkyl group; R_2 is hydrogen and R_1 is an optionally substituted aryl or an arylalkyl or heterocyclyl-alkyl group with from 1 to 4 carbon atoms within the alkyl chain.

Another class of preferred compounds of the invention are the compounds of formula (I)



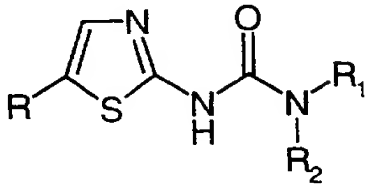
(I)

wherein

R is a halogen atom or is selected from the group consisting of nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl, straight or branched C_1-C_6 alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy, aryl optionally substituted

CLAIMS

1. The use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

i) straight or branched C_1-C_6 alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound;

or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for treating cell proliferative disorders associated with an altered cell dependent kinase activity.

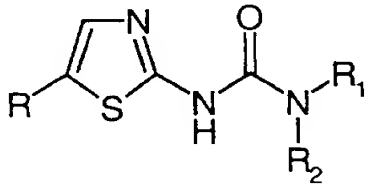
2. Use according to claim 1 wherein the said cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative disorders.

3. Use according to claim 2 wherein the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. Use according to claim 1 wherein the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

5. Use according to any one of the preceding claims wherein the medicament enables tumor angiogenesis and metastasis inhibition.

6. A compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

i) straight or branched C_1-C_6 alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

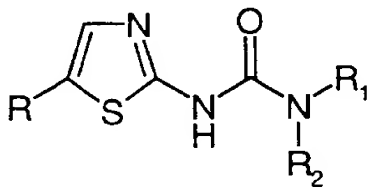
ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

for use as a medicament; provided that:

a) when R is a chlorine atom and R_2 is hydrogen, then R_1 is not methyl, phenyl or trifluoromethylphenyl; and

b) when R is methyl and R_2 is hydrogen, then R_1 is not 4-(5-oxazolyl)phenyl.

7. A compound which is a 2-amino-1,3-thiazole derivative of formula (I)



(I)

wherein

P ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 13 June 2000 (13.06.00)	
International application No. PCT/EP99/08307	**Applicant's or agent's file reference** FC 858/5
International filing date (day/month/year) 27 October 1999 (27.10.99)	**Priority date** (day/month/year) 30 October 1998 (30.10.98)
Applicant PEVARELLO, Paolo et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 May 2000 (15.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Claudio Borton
Facsimile No.: (41-22) 740 14 35	Telephone No.: (41-22) 338 83 38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PHARMACIA & UPJOHN SPA
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

Date of mailing (day/month/year) 03 December 1999 (03.12.99)	
Applicant's or agent's file reference FC 858/5	**IMPORTANT NOTIFICATION**
International application No. PCT/EP99/08307	International filing date (day/month/year) 27 October 1999 (27.10.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 30 October 1998 (30.10.98)
Applicant PHARMACIA & UPJOHN S.P.A. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
30 Octo 1998 (30.10.98)	9823873.6	GB	26 Nove 1999 (26.11.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

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Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:
PHARMACIA & UPJOHN SPA
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 11 May 2000 (11.05.00)	
Applicant's or agent's file reference FC 858/5	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP99/08307	27 October 1999 (27.10.99)	30 October 1998 (30.10.98)

Applicant
PHARMACIA & UPJOHN S.P.A. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
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   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AP,BA,BB,BG,BR,CA,CU,CZ,EA,EE,EP,GD,GE,HR,HU,ID,IL,IN,IS,LC,LK,LR,LT,LV,MG,MK,MN,MX,NO,NZ,OA,PL,RO,SG,SI,SK,SL,TR,TT,UA,UZ,VN,YU,ZA

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   11 May 2000 (11.05.00) under No. WO 00/26203

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
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Form PCT/IB/308 (July 1996)

3261671

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 277/48, 417/12, 417/14, 471/10, 491/10, A61K 31/426, 31/427, C07D 471/04 // (C07D 471/10, 235:00, 221:00) (C07D 491/10, 317:00, 221:00) (C07D 471/04, 235:00, 221:00)

A1

(11) International Publication Number: **WO 00/26203**

(43) International Publication Date: 11 May 2000 (11.05.00)

(21) International Application Number: PCT/EP99/08307

(22) International Filing Date: 27 October 1999 (27.10.99)

(30) Priority Data:
9823873.6 30 October 1998 (30.10.98) GB

30 Apr 01 / 30 mos

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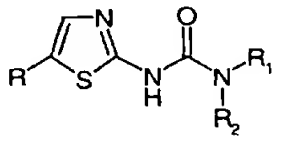
(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 2–UREIDO–THIAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND THEIR USE AS ANTITUMOR AGENTS



(I)

(57) Abstract

Compounds which are 2–ureido–1, 3–thiazole derivatives of formula (I) wherein R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from: i) straight or branched C_1–C_6 alkyl; ii) C_3–C_6 cycloalkyl; iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain; R_1 is an optionally substituted group selected from i) straight or branched C_1–C_6 alkyl; ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring; iii) aryl or arylcarbonyl; iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain; R_2 is hydrogen, a straight or branched C_1–C_4 alkyl or C_2–C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded, R_1 and R_2 form a substituted or unsubstituted group selected from: i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or ii) a 9 to 11 membered spiro–heterocyclic compound; or a pharmaceutically acceptable salt thereof; are useful for treating cell proliferative disorders associated with an altered cell dependent kinase activity.

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R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

i) straight or branched C_1-C_6 alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

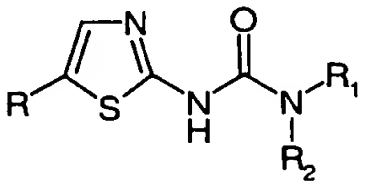
ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

for use as a medicament; provided that:

a) when R is a chlorine atom and R_2 is hydrogen, then R_1 is not methyl, phenyl or trifluoromethylphenyl; and

b) when R is methyl and R_2 is hydrogen, then R_1 is not 4-(5-oxazolyl)phenyl.

7. A compound which is a 2-amino-1,3-thiazole derivative of formula (I)



(I)

wherein

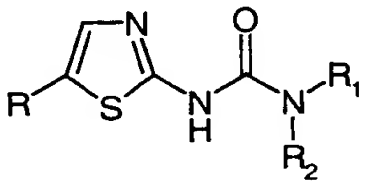
2. Use according to claim 1 wherein the said cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases or neurodegenerative disorders.

3. Use according to claim 2 wherein the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

4. Use according to claim 1 wherein the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis and restenosis.

5. Use according to any one of the preceding claims wherein the medicament enables tumor angiogenesis and metastasis inhibition.

6. A compound which is a 2-ureido-1,3-thiazole derivative of formula (I)

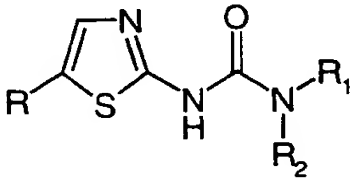


(I)

wherein

CLAIMS

1. The use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

i) straight or branched C_1-C_6 alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound;

or a pharmaceutically acceptable salt thereof; in the manufacture of a medicament for treating cell proliferative disorders associated with an altered cell dependent kinase activity.

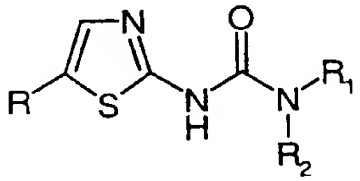
The compounds of formula (I) may have asymmetric carbon atoms and may therefore exist either as racemic admixtures or as individual optical isomers.

Accordingly, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

Preferred compounds of the invention are the compounds of formula (I) wherein R is a halogen atom, a straight or branched C_1-C_4 alkyl group, a phenyl or a cycloalkyl group; R_2 is hydrogen and R_1 is an optionally substituted group selected from alkyl, aryl or arylakyl.

Even more preferred, within this class, are the compounds of formula (I) wherein R is bromine or chlorine, a straight or branched C_1-C_4 alkyl group, a phenyl or a cycloalkyl group; R_2 is hydrogen and R_1 is an optionally substituted aryl or an arylalkyl or heterocyclyl-alkyl group with from 1 to 4 carbon atoms within the alkyl chain.

Another class of preferred compounds of the invention are the compounds of formula (I)



(I)

wherein

R is a halogen atom or is selected from the group consisting of nitro, amino, alkylamino, hydroxyalkylamino, arylamino, C_3-C_6 cycloalkyl, straight or branched C_1-C_6 alkyl optionally substituted by hydroxy, alkylthio, alkoxy, amino, alkylamino, alkoxycarbonylalkylamino, alkylcarbonyl, alkylsulfonyl, alkoxycarbonyl, carboxy, aryl optionally substituted

iv) arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_2 is hydrogen, a straight or branched C_1-C_4 alkyl or C_2-C_4 alkenyl or alkynyl group; or, taken together with the nitrogen atom to which they are bonded,

R_1 and R_2 form a substituted or unsubstituted group selected from:

i) an optionally benzocondensed or bridged 5 to 7 membered heterocycle; or

ii) a 9 to 11 membered spiro-heterocyclic compound; or a pharmaceutically acceptable salt thereof;

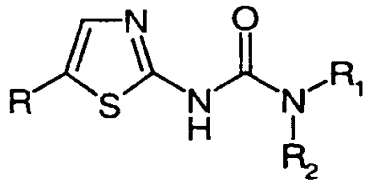
for use as a medicament; provided that:

a) when R is a chlorine atom and R_2 is hydrogen, then R_1 is not methyl, phenyl or trifluoromethylphenyl; and

b) when R is methyl and R_2 is hydrogen, then R_1 is not 4-(5-oxazolyl)phenyl.

Among the compounds of formula (I) above reported, several derivatives result to be novel.

Therefore, the present invention further provides a compound which is a 2-amino-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

iii) C_3-C_6 cycloalkyl;

iv) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

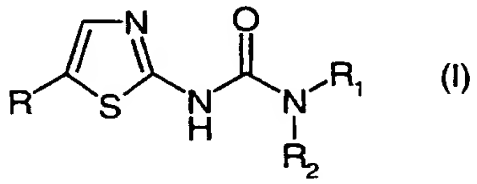
R_1 is an optionally further substituted group selected from:

glomerulonephritis and post-surgical stenosis and restenosis.

In addition, being useful in the treatment of cell proliferative disorders associated with an altered cell dependent kinase activity, hence cell cycle inhibition or cdk/cyclin dependent inhibition, the compounds of formula (I) of the invention also enable tumor angiogenesis and metastasis inhibition.

As above reported, some of the compounds of formula (I) of the invention have been reported in the art as useful therapeutic agents, for instance as antiinflammatory, sedative and analgesic agents.

Therefore, it is a further object of the present invention a compound which is a 2-ureido-1,3-thiazole derivative of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

i) straight or branched C_1-C_6 alkyl;

ii) 3 to 6 membered carbocycle or 5 to 7 membered heterocycle ring;

iii) aryl or arylcarbonyl;

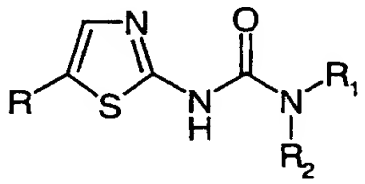
reference, US 3,726,891 in the name of Shell Co., and C.A. 83(1975):114381].

Just few examples among them are N'-methyl- and N'-ehtyl-N-(5-bromo-2-thiazolyl)-urea; N'-methyl-, N'-ethyl- or N'-phenyl-N-(5-chloro-2-thiazolyl)-urea; N-(5-chloro-2-thiazolyl)-N',N'-dimethyl-urea; N-(5-bromo-2-thiazolyl)-N',N'-dimethyl-urea; N'-methyl- and N'-phenyl-N-(5-methyl-2-thiazolyl)-urea.

Other 2-ureido-1,3-thiazole derivatives have been described in the art as therapeutic agents.

Among them are N-methyl- and N-phenyl-N'-(5-chloro-2-thiazolyl)-urea which have been described as sedative and antiinflammatory agents in FR M. 7428 (Melle-bezons) or N-[4-(5-oxazolyl)phenyl]-N'-(5-methyl-2-thiazolyl)-urea, described as inosine 5'-monophosphate dehydrogenase inhibitor (IMPDH) in WO 97/40028 (Vertex Pharmaceuticals Inc.).

Accordingly, the present invention provides the use of a compound which is a 2-ureido-1,3-thiazole derivatives of formula (I)



(I)

wherein

R is a halogen atom, a nitro group, an optionally substituted amino group or it is a group, optionally further substituted, selected from:

i) straight or branched C_1-C_6 alkyl;

ii) C_3-C_6 cycloalkyl;

iii) aryl or arylalkyl with from 1 to 6 carbon atoms within the straight or branched alkyl chain;

R_1 is an optionally further substituted group selected from:

i) straight or branched C_1-C_6 alkyl;

VERTRAG UBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS

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INTERNATIONALER RECHERCHENBERICHT

(Artikel 18 sowie Regeln 43 und 44 PCT)

Aktenzeichen des Anmelders oder Anwalts	**WEITERES VORGEHEN**	siehe Mitteilung über die Übermittlung des internationalen Recherchenberichts (Formblatt PCT/ISA/220) sowie, soweit zutreffend, nachstehender Punkt 5	
FC 858/5			
Internationales Aktenzeichen	Internationales Anmeldedatum *(Tag/Monat/Jahr)*	(Frühestes) Prioritätsdatum *(Tag/Monat/Jahr)*	
PCT/EP 99/ 08307	27/10/1999	30/10/1998	
Anmelder			
PHARMACIA & UPJOHN S.P.A. et al.			

Dieser internationale Recherchenbericht wurde von der Internationalen Recherchenbehörde erstellt und wird dem Anmelder gemäß Artikel 18 übermittelt. Eine Kopie wird dem Internationalen Büro übermittelt.

Dieser internationale Recherchenbericht umfaßt insgesamt 4 Blätter.

[X] Darüber hinaus liegt ihm jeweils eine Kopie der in diesem Bericht genannten Unterlagen zum Stand der Technik bei.

1. **Grundlage des Berichts**

   a. Hinsichtlich der **Sprache** ist die internationale Recherche auf der Grundlage der internationalen Anmeldung in der Sprache durchgeführt worden, in der sie eingereicht wurde, sofern unter diesem Punkt nichts anderes angegeben ist.

   [ ] Die internationale Recherche ist auf der Grundlage einer bei der Behörde eingereichten Übersetzung der internationalen Anmeldung (Regel 23.1 b)) durchgeführt worden.

   b. Hinsichtlich der in der internationalen Anmeldung offenbarten **Nucleotid- und/oder Aminosäuresequenz** ist die internationale Recherche auf der Grundlage des Sequenzprotokolls durchgeführt worden, das

   [ ] in der internationalen Anmeldung in Schriftlicher Form enthalten ist.

   [ ] zusammen mit der internationalen Anmeldung in computerlesbarer Form eingereicht worden ist.

   [ ] bei der Behörde nachträglich in schriftlicher Form eingereicht worden ist.

   [ ] bei der Behörde nachträglich in computerlesbarer Form eingereicht worden ist.

   [ ] Die Erklärung, daß das nachträglich eingereichte schriftliche Sequenzprotokoll nicht über den Offenbarungsgehalt der internationalen Anmeldung im Anmeldezeitpunkt hinausgeht, wurde vorgelegt.

   [ ] Die Erklärung, daß die in computerlesbarer Form erfaßten Informationen dem schriftlichen Sequenzprotokoll entsprechen, wurde vorgelegt.

2. [ ] **Bestimmte Ansprüche haben sich als nicht recherchierbar erwiesen** (siehe Feld I).

3. [ ] **Mangelnde Einheitlichkeit der Erfindung** (siehe Feld II).

4. Hinsichtlich der **Bezeichnung der Erfindung**

   [X] wird der vom Anmelder eingereichte Wortlaut genehmigt.

   [ ] wurde der Wortlaut von der Behörde wie folgt festgesetzt:

5. Hinsichtlich der **Zusammenfassung**

   [X] wird der vom Anmelder eingereichte Wortlaut genehmigt.

   [ ] wurde der Wortlaut nach Regel 38.2b) in der in Feld III angegebenen Fassung von der Behörde festgesetzt. Der Anmelder kann der Behörde innerhalb eines Monats nach dem Datum der Absendung dieses internationalen Recherchenberichts eine Stellungnahme vorlegen.

6. Folgende Abbildung der **Zeichnungen** ist mit der Zusammenfassung zu veröffentlichen: Abb. Nr. –

   [ ] wie vom Anmelder vorgeschlagen

   [ ] weil der Anmelder selbst keine Abbildung vorgeschlagen hat.

   [ ] weil diese Abbildung die Erfindung besser kennzeichnet.

   [ ] keine der Abb.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10376

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/363, 371, 407, 415, 422, 426, 427, 438, 444, 447, 448; 548/128, 196, 365.7, 491, 527, 532; 549/59, 69, 71; 564/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96/40673 A1 (SUGEN INC) 19 December 1996, page 87, lines 1-14, 16-19; page 88, lines 1-17.	1-17
Y	Database CA on STN, EP 676395 A2 (Hoechst A.-G., Germany), No. 124:86809, KLEEMANN et al., 'Preparation of (pyrrolyl- and thienylcarbonyl)guanidines as sodium-hydrogen exchange inhibitors, antiarrhythmic agents, and cell proliferation inhibitors.' abstract, Hanno Wild, 17 July 1996.	1-14
A	US 5,597,719 A (FREED et al.) 28 January 1997, entire document.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search 17 JUNE 1998	Date of mailing of the international search report 30 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANE C. OSWECKI Telephone No. (703)308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10376

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/34, 31/38, 31/385, 31/40, 31/405, 31/415, 31/425; C07C 275/26; C07D 207/30, 209/08, 231/38, 277/44, 285/135, 307/52, 409/12, 411/12, 417/12

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/363, 371, 407, 415, 422, 426, 427, 438, 444, 447, 448; 548/128, 196, 365.7, 491, 527, 532; 549/59, 69, 71; 564/48

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE, CASLINK, MARPAT, BEILSTEIN, BIOSIS, MEDLINE
search terms: cancer, oncolog?, tumor, cell proliferat?, cell growth, thien?, furan, pyrrol?, urea, amide?, ester, raf?, kinase?

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/08307

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/48 C07D417/12 C07D417/14 C07D471/10 C07D491/10
A61K31/426 A61K31/427 C07D471/04 //(C07D471/10,235:00,
221:00),(C07D491/10,317:00,221:00),(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 7 428 M (MELLE-BEZONS) 12 November 1969 (1969-11-12) the whole document	6-16
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X	DE 20 40 580 A (MAY & BAKER LTD) 22 April 1971 (1971-04-22) claims	6-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2000	04/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
X	LESLIE M. WERBEL ET AL: "1-Alkyl-3-(3-alkyl-5-nitro-4-thiazolin-2-ylidene)ureas and related compounds as schistomicides" JOURNAL OF MEDICINAL CHEMISTRY., vol. 15, no. 9, 1972, pages 955-963, XP002128090 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 the whole document	6-16
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Information on patent family members

International Application No
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/34, 31/38, 31/385, 31/40, 31/405, 31/415, 31/425, C07C 275/26, C07D 207/30, 209/08, 231/38, 277/44, 285/135, 307/52, 409/12, 411/12, 417/12

A1

(11) International Publication Number: **WO 98/52559**

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/US98/10376

(22) International Filing Date: 21 May 1998 (21.05.98)

(30) Priority Data:
08/863,021 23 May 1997 (23.05.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 08/863,021 (CIP)
Filed on 23 May 1997 (23.05.97)

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(74) Agents: SHUBIN, Harry, B. et al.; Millen, White, Zelano & Branigan, P.C., Arlington Courthouse Plaza I, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: RAF KINASE INHIBITORS

(57) Abstract

Methods of treating tumors mediated by raf kinase, with substituted urea compounds, and such compounds per se.

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RAF KINASE INHIBITORS

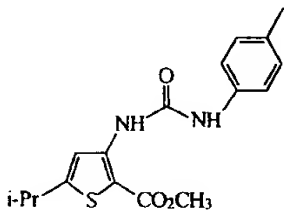
Background of the Invention

The $p21^{ras}$ oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30% of all human cancers; Bolton et al., Annual Reports in Medicinal Chemistry, 29, 165-174 (1994); Bos, Cancer Res., 49, 4682 (1989).

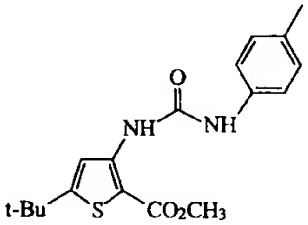
In its normal, unmutated form, the ras protein is a key element of the signal transduction cascade directed by growth factor receptors in almost all tissues. See J. Avruch et al., TIBS (19), 279-283 (1994). Biochemically, ras is a guanine nucleotide binding protein, and cycling between a GTP-bound activated and a GDP-bound resting form is strictly controlled by ras' endogenous GTPase activity and other regulatory proteins. In the ras mutants in cancer cells, the endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells which carry these mutants, Magnuson et al., Cancer Biology, 5, 247-253 (1994). It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK, the substrate of raf kinase, leads to the reversion of transformed cells to the normal growth phenotype. See Daum et al., TIBS 19, 474-480 (1994), and Fridman et al., J. Biol. Chem., 269, 30105-30108 (1994). Kolch et al., Nature, 349, 426-428 (1991), have further indicated that inhibition of raf expression by antisense RNA blocks cell proliferation in membrane-associated oncogenes. Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types; Monia et al., Nature Medicine, 2(6):668-675 (1996).

Summary of the Invention

The present invention is directed to compounds and methods for the treatment of cancerous cell growth mediated by raf kinase. The compounds of the formulae



5-Isopropyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid methyl ester



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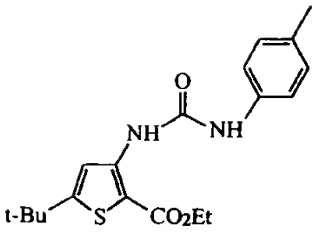

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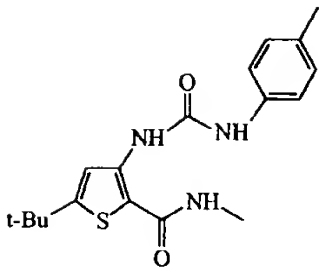

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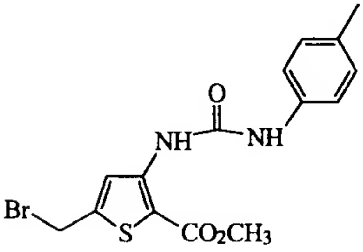

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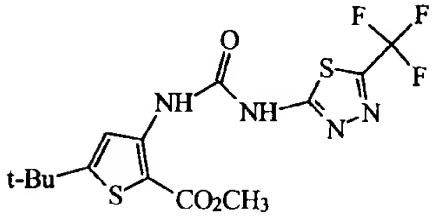

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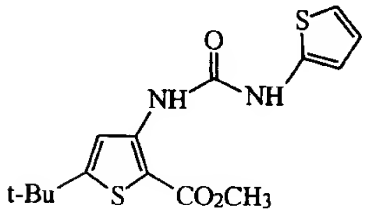

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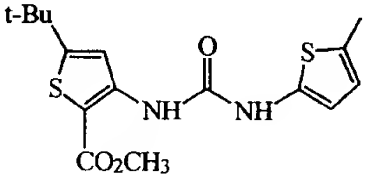

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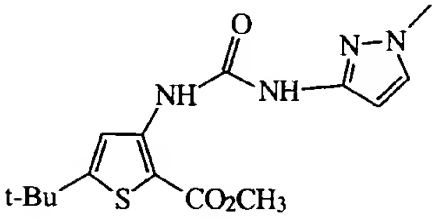

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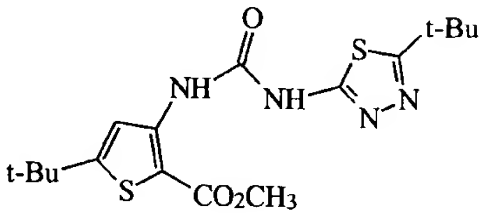

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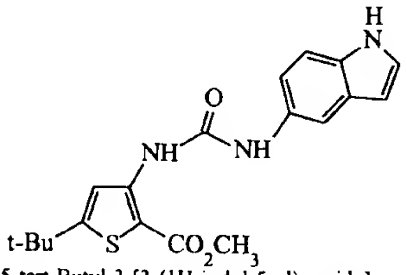

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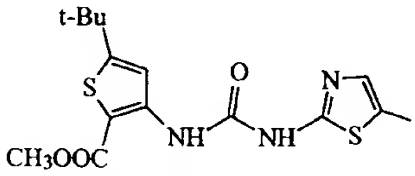

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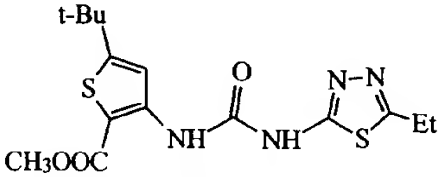

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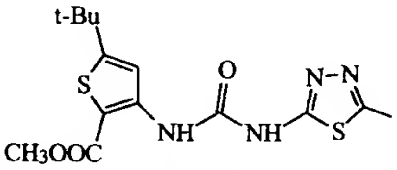

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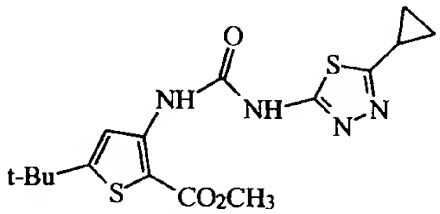
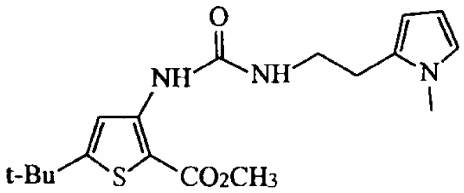


5-tert-Butyl-3-[3-(5-cyclopropyl-[1,3,4]thiadiazol-2-yl)ureido]-thiophene-2-carboxylic acid methyl ester



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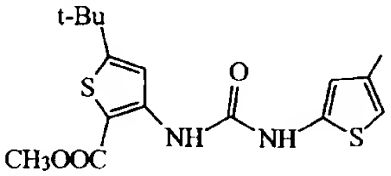

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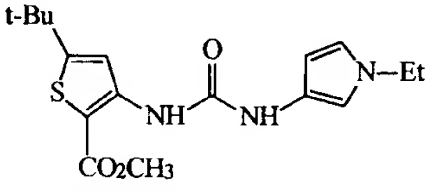

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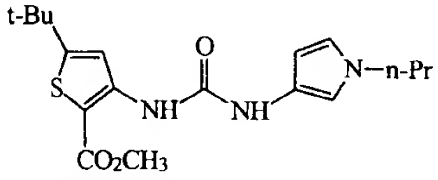

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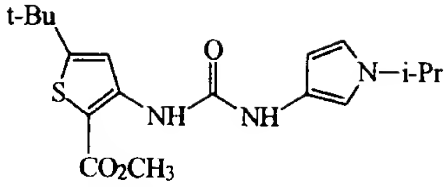

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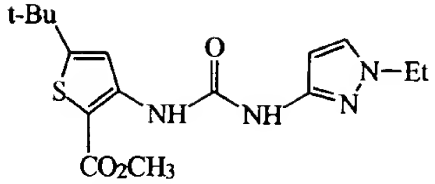

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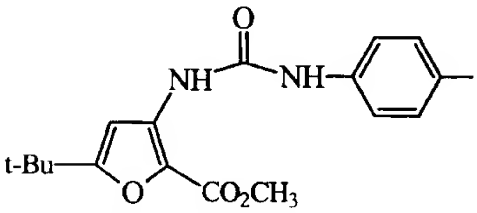
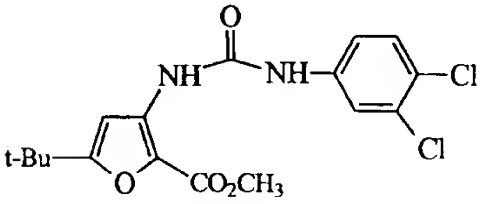


5-tert-Butyl-3-(3-p-tolyl-ureido)-furan-2-carboxylic acid methyl ester



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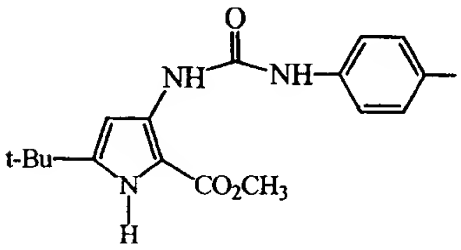

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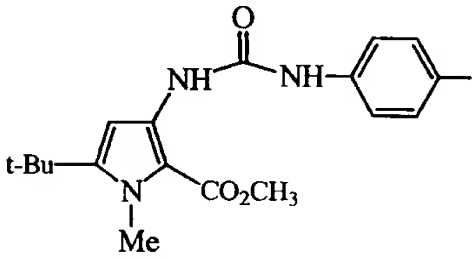

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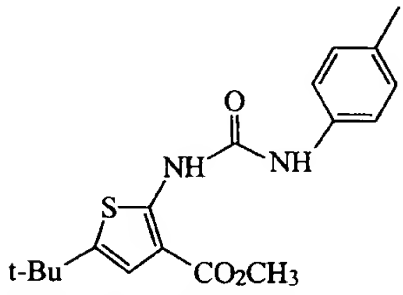
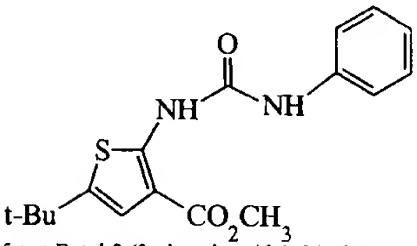


5-tert-Butyl-2-(3-p-tolyl-ureido)-thiophene-3-carboxylic acid methyl ester



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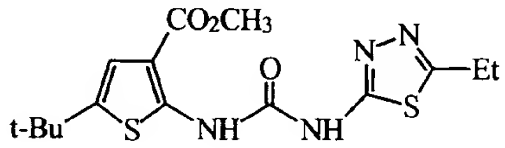
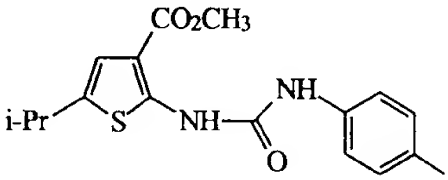
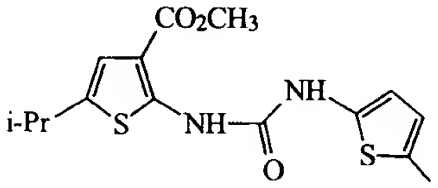


5-tert-Butyl-2-(3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-ureido)-thiophene-3-carboxylic acid methyl ester



5-Isopropyl-2-(3-p-tolyl-ureido)-thiophene-3-carboxylic acid methyl ester

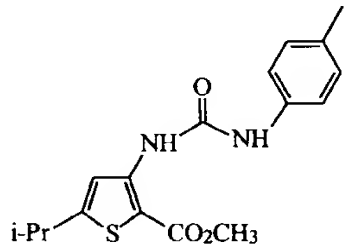
or

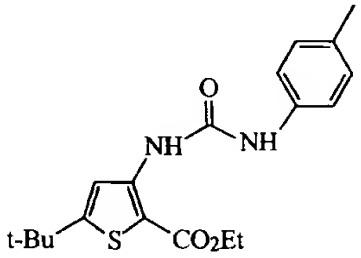


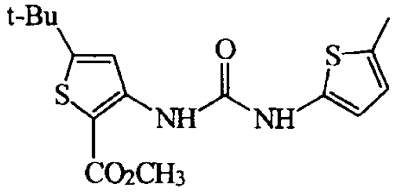
5-Isopropyl-2-[3-(5-methyl-thiophen-2-yl)-ureido]-thiophene-3-carboxylic acid methyl ester

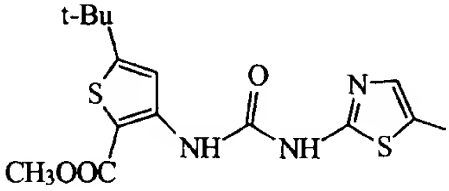
(where Et is ethyl, Pr is propyl, and Bu is butyl).

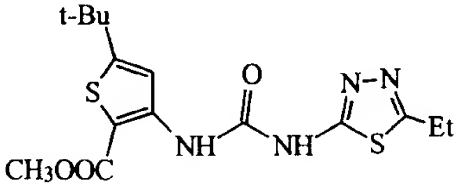
Preferred compounds include, e.g.,

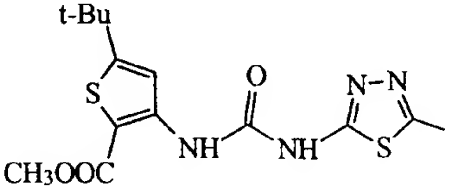


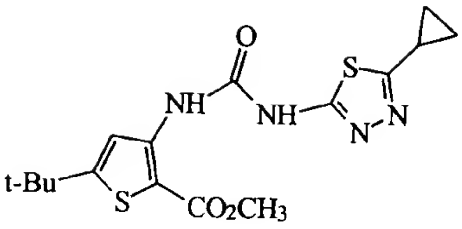
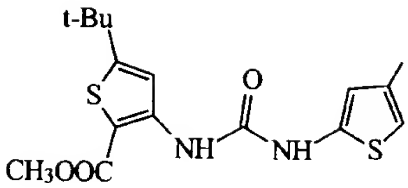
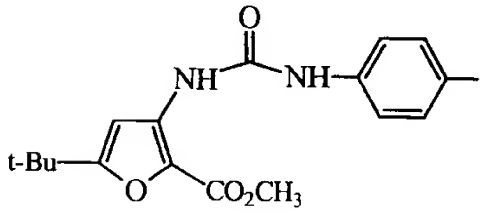
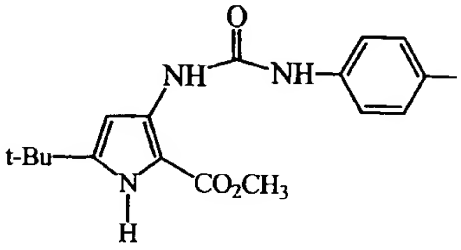
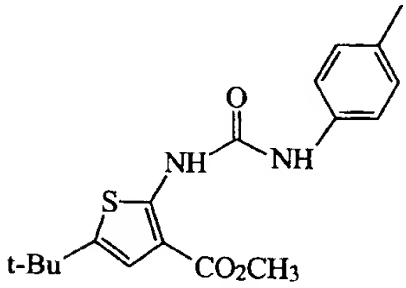
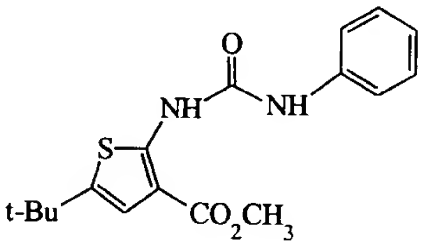






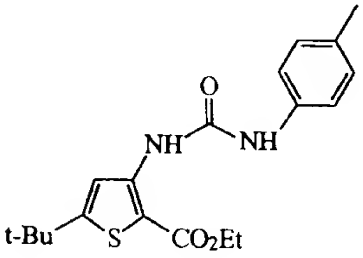
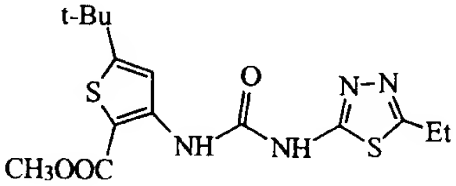
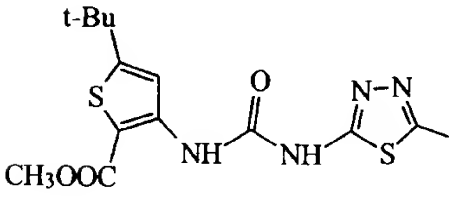
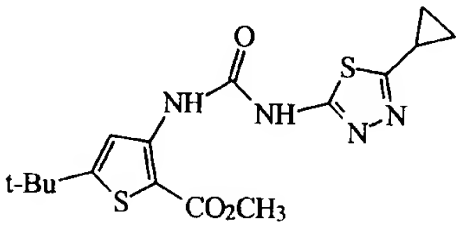


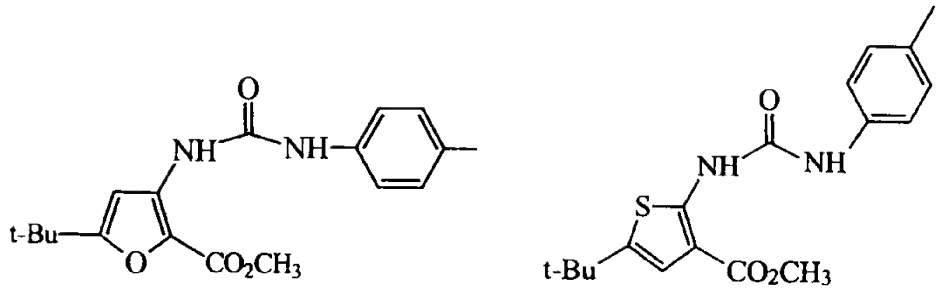


;

more preferably,



The compounds may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and if desired other active ingredients. The preferred method of administration is parenteral.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; and binding agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products or an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and

esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The compounds may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics.

The compounds of the invention are typically employed at a dosage of 0.01 to 200 mg/kg per day, preferably 200 mg/kg ip.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the condition undergoing therapy.

The compounds of the invention are inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of $p21^{ras}$, the instant inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal, e.g., murine, solid cancers, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by interruption of the cascade, i.e., by inhibiting raf kinase.

The activity of a given compound to inhibit raf kinase can be routinely assayed, e.g., according to procedures disclosed herein.

In such an in vitro kinase assay, raf is incubated with MEK in 20 mM Tris-HCl, pH 8.2 containing 2 mM 2-mercaptoethanol and 100 mM NaCl. Twenty microliters of this protein solution are mixed with 5 µl of water or compounds diluted with distilled water from 10 mM stock solutions of compounds dissolved in DMSO. The kinase reaction is initiated by adding 25 µl [γ-^{33}P]ATP (1000-3000 dpm/pmol) in 80 mM Tris-HCl, pH 7.5, 120 mM NaCl, 1.6 mM DTT, 16 mM $MgCl_2$. The reaction mixtures are incubated at 32°C, usually for 22 minutes and incorporation of ^{33}P into protein is assayed by harvesting the reaction onto phosphocellulose mats, washing away free counts with 1% phosphoric acid and quantitating phosphorylation by liquid scintillation counting. For high throughput screening, 10 µM ATP and 0.4 µM MEK are used. In some experiments, the kinase reaction is stopped by adding an equal amount of Laemmli sample buffer. Samples are boiled 3 minutes and the proteins resolved by electrophoresis on 7.5% Laemmli gels. Gels are fixed, dried and exposed to an imaging plate (Fuji). Phosphorylation is analyzed using a Fujix Bio-Imaging Analyzer System. Protein kinase C (0.05 mU; Boehringer Mannheim) phosphorylation of histone H1 is assayed according to manufacturer's instructions.

For in vitro growth assay, untransformed NIH3T3 fibroblast or transformed fibroblasts stably expressing their v-H-ras, v-Raf or v-fos are obtained (Onyx). The fibroblast lines are maintained in Dulbecco's Modified Eagle's Medium with high glucose containing 10% fetal bovine serum and 200 mM glutamine. Human colon carcinoma cell lines, DLD-1, Colo 205 and HCT116 are obtained from ATCC (Rockville, MD) and maintained in RPMI with 10% fetal bovine serum and 200 mM glutamine. Cell culture media and additives are obtained from Gibco/BRL (Gaithersburg, MD) except for fetal bovine serum (JRH Biosciences, Lenexa, KS). In some experiments, 3 x 10^3 cells are seeded into 96-well plates and allowed to grow overnight at 37°C in a 5% CO_2 incubator. Proliferation is determined by allowing the cells to incorporate ^{3}H-thymidine during the last 18 hours of culture, harvesting cells onto glass fiber mats and measuring ^{3}H-thymidine incorporation by liquid scintillation counting.

These assays establish that the compounds of formula I are active to inhibit raf kinase activity and to inhibit oncogenic cell growth.

An in vivo assay of the inhibitory effect of the compounds on tumors (e.g., solid cancers) mediated by raf kinase can be performed as follows:

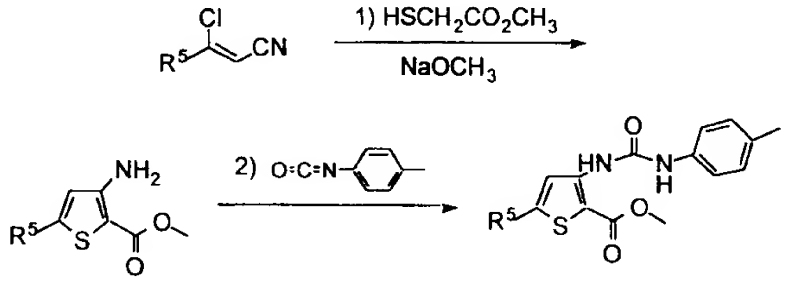
CDI nu/nu mice (6-8 weeks old) are injected subcutaneously into the flank at 1 x 10^6 cells with human colon adenocarcinoma cell line . The mice are dosed ip at 50, 100, and 200 mg/kg beginning on day 10, when tumor size is between 50-100 mg. Animals are dosed for 10 consecutive days once a day; tumor size was monitored with calipers twice a week to day 35.

The inhibitory effect of the compounds on raf kinase and therefore on tumors (e.g., solid cancers) mediated by raf kinase can further be demonstrated in vivo according to the technique of Monia et al., Nature Medicine, 2(6):668-675 (1996).

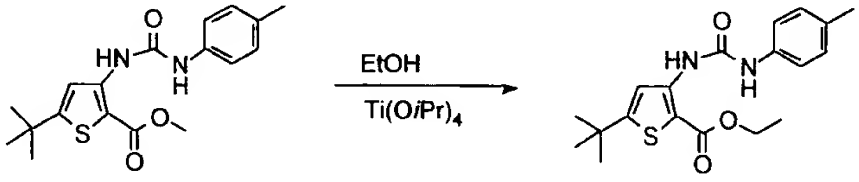
Accordingly, the compounds of the invention are useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon, myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).

The compounds of formulae 1-31 are producible from known compounds (or from starting materials which, in turn, are producible from known compounds), e.g., through the general preparative methods shown below:

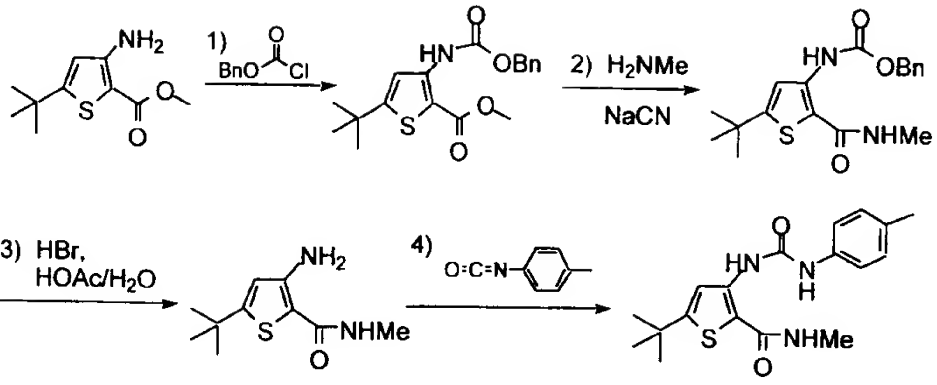
Method A



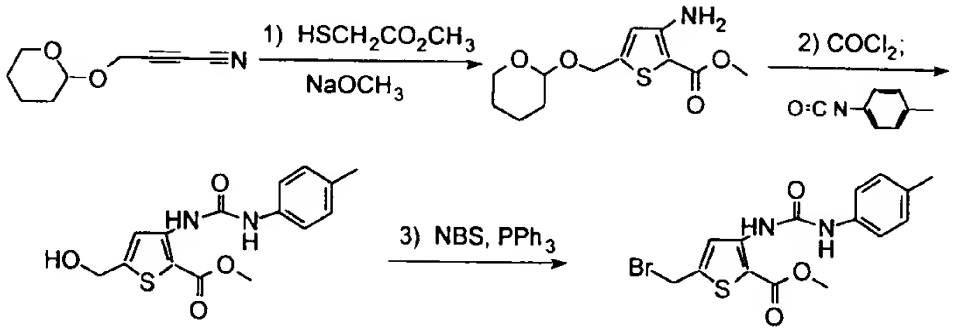
Method B



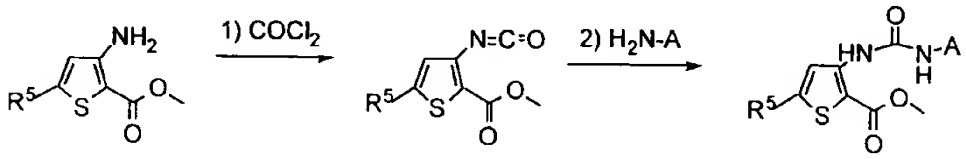
Method C



Method D



Method E



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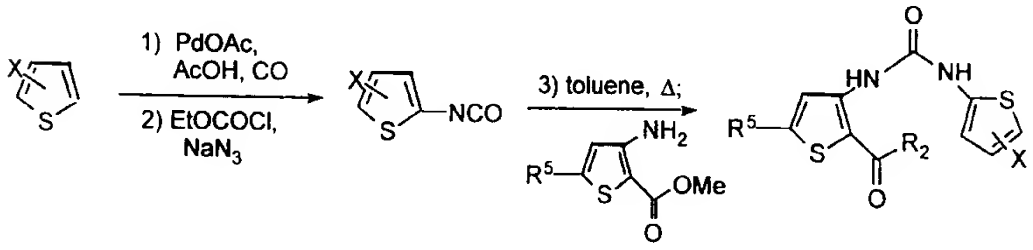
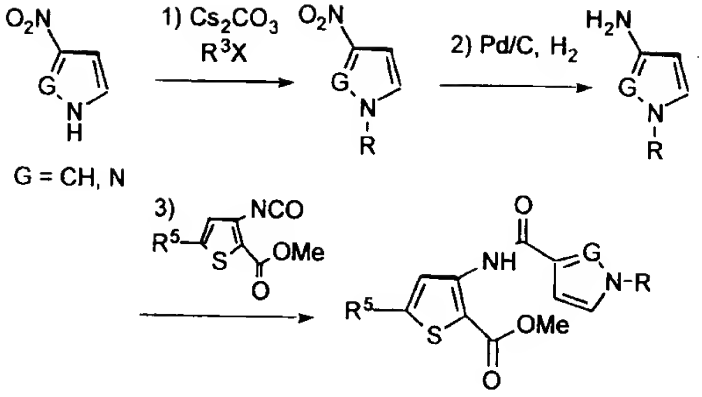
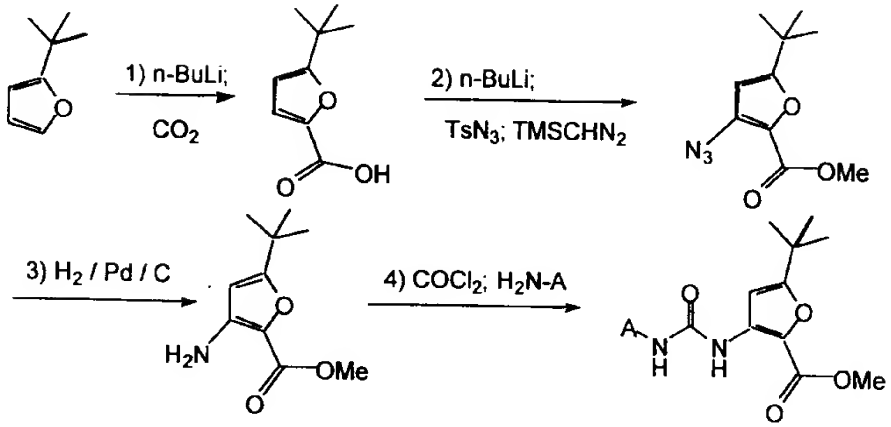


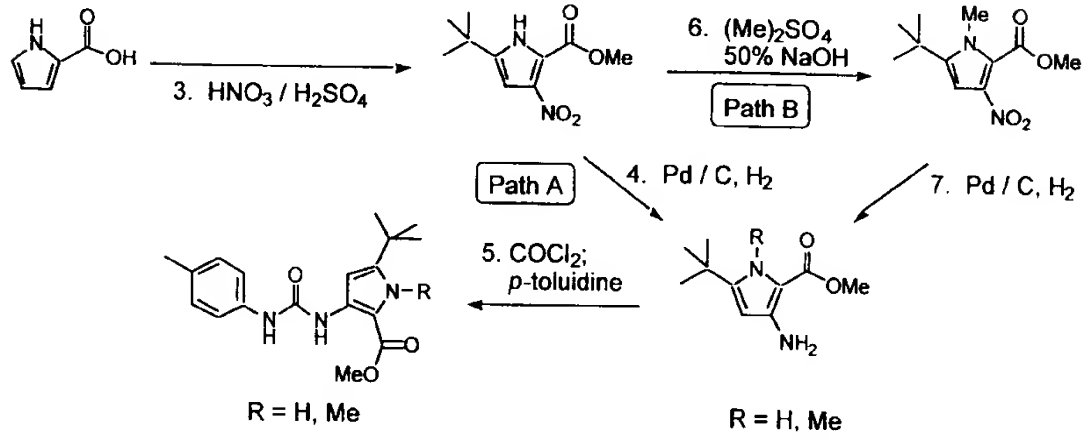
Method G



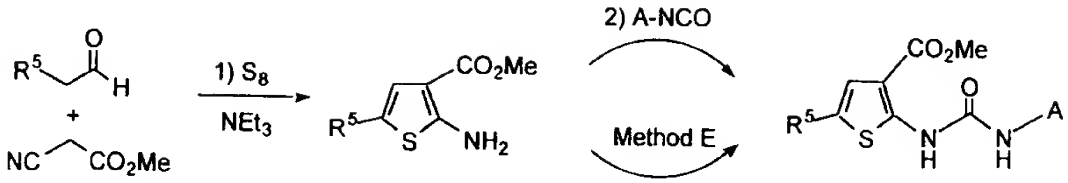
Method H



Method I



Method J



Abbreviations used:

Ac, acetyl; Ar, aryl; Boc, t-butoxycarbonyl; Bn, benzyl; Cbz, carbobenzyloxy; DCC, dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; DMF, N,N-di-ethylformamide; Et, ethyl; EtOAc, ethyl acetate; LRMS, low resolution mass spectrometry; Me, methyl; NMM, N-methyl morpholine; Ph, phenyl; Pr, propyl; pyr., pyridine; TLC, thin layer chromatography; TFA, trifluoroacetic acid; TMS, trimethylsilyl; Ts, p-toluenesulfonyl.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and, unless otherwise indicated, all parts and percentages are by volume.

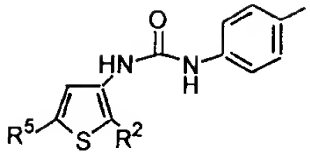
The entire disclosure of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

EXAMPLES

Experimental:

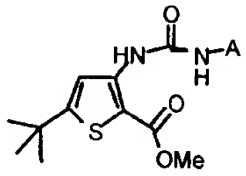
Flash chromatography was run using Silica Gel 60 (230-400 mesh size) from EM Science. Mass spectral data were obtained on a Krato-MS 80RFA spectrometer using the fast atom bombardment technique (FAB) unless otherwise noted. Melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are not corrected.

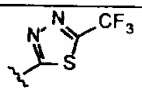
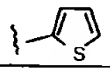
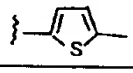
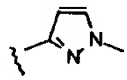
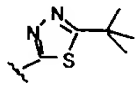
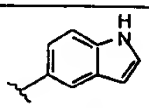
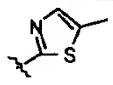
Table 1. 3-Ureido Thiophenes



Example #	R^5	R^2	Method	mp °C or LRMS
1	i-Pr	COOMe	A	93-95
2	t-Bu	COOMe	A	124-126
3	t-Bu	COOEt	B	$(M+H)^+ = 361$
4	t-Bu	CONHMe	C	230-231
5	CH_2Br	COOMe	D	157-158

Table 2. Heteroaryl substitution for A



Example #	A	Method	mp °C or LRMS
6		E	$(M+H)^+ = 409$
7		F	$(M+H)^+ = 339$
8		F	$(M+H)^+ = 353$
9		E	186-188
10		E	$(M+H)^+ = 397$
11		E	$(M+H)^+ = 372$
12		E	215-216

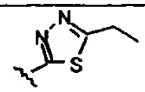
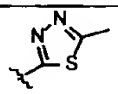
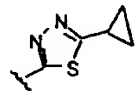
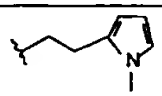
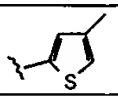
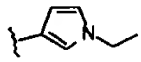
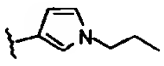
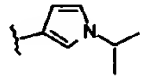
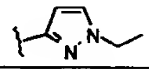
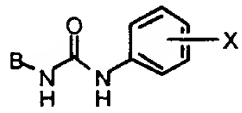
13		E	168-170
14		E	229-231
15		E	$(M+H)^+ = 381$
16		E	$(M+H)^+ = 364$
17		F	$(M+H)^+ = 353$
18		G	$(M+H)^+ = 350$
19		G	$(M+H)^+ = 364$
20		G	$(M+H)^+ = 364$
21		G	$(M+H)^+ = 351$

Table 3. Furyl or pyrrole substitution for B.



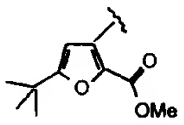
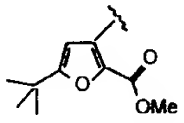
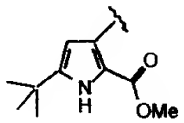
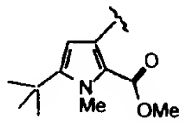
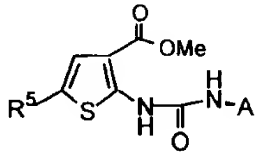
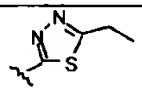
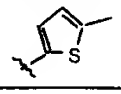
Example #	B	X	Method	LRMS
22		4-Me	H	$(M+H)^+ = 331$
23		3,4-diCl	H	$M^+ = 384$ EI
24		4-Me	I	$(M+H)^+ = 330$
25		4-Me	I	$M^+ = 343$

Table 4. 2-Ureido Thiophenes

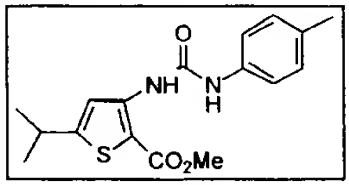


Example #	R^5	A	Method	mp °C
26	t-Bu	4-Me-Ph	J	109-111
27	t-Bu	Ph	J	80-82
28	t-Bu		J	206-208
29	iPr	4-Me-Ph	J	49-51
30	iPr		J	70-73

The following compounds have been synthesized according to the general methods listed above:

Method A

Synthesis of 5-Isopropyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid methyl ester. (Example 1)



Step 1

To a suspension of sodium methoxide (14 g) in methanol (1 L) was added methyl thioglycolate (22.3 mL). The solution was stirred 5 min, then 3-chloro-4-methyl-2-pentenenitrile (32.4 g) [Hackler, R. E. et al. J. Heterocyclic Chem. 1989, 26, 1575; Hartmann, H.; Liebscher, J. Synthesis 1984, 275; Gupton, J. T. et al. Synthetic Comm. 1982, 12, 34] in methanol (200 mL) was added and the solution was heated to reflux for 90 min. After cooling to 20 °C, the solvent was removed in vacuo. The residue was dissolved in ethyl acetate and was washed with 1N HCl, dried over

$MgSO_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography using hexane/ethyl acetate mixtures to yield 8.0 g (16%) of the desired amino thiophene.

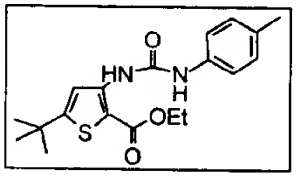
Step 2

A solution of 3-amino-5-isopropyl-2-methyl ester-thiophene (233 mg) in toluene (10 mL) was heated to reflux. A solution of p-methylphenyl isocyanate (150 uL) in toluene (5 mL) was added via a syringe pump over 1 h. The reaction was heated to reflux for 1 h, cooled to 20 °C and the solvent removed in vacuo. The residue was purified by flash chromatography using hexane/dichloromethane mixtures to yield 265 mg (68%) of Example 1 as a foam. ^{1}H NMR ($CDCl_3$) d 1.28 (s, 6H), 2.30 (s, 3H), 3.06 (m, 1H), 3.75 (s, 3H), 7.11 (d, 2H), 7.30 (d, 2H), 7.72 (s, 1H), 7.83 (s, 1H), 9.67 (s, 1H).

5-tert-Butyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid methyl ester (example 2) was synthesized according to this procedure using 3-chloro-4,4-dimethyl-2-pentenenitrile in place of the 3-chloro-4-methyl-2-pentenenitrile.

Method B

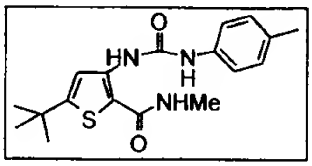
Synthesis of 5-tert-Butyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid ethyl ester. (Example 3)



A solution of titanium isopropoxide (1 mL), methyl 3-(4-methyl phenyl urea)-5-tert-butyl thiophene-2-carboxylate (500 mg, 1.44 mmol), and ethanol (10 mL) was heated to for 24 h. Solvent was removed in vacuo and the resultant oil was dissolved in methylene chloride and purified by flash chromatography (ethyl acetate/hexane). Concentration in vacuo afforded 119 mg (23%) of Example 3. ^{1}H NMR ($CDCl_3$) d 9.71 (s, 1H); 7.87 (s, 1H); 7.29 (d, J= 8.5Hz, 2H); 7.15 (d, J= 8.1Hz, 2H); 4.28 (q, J=7.4Hz, 2H); 2.33 (s, 3H); 1.29 (m, 12H).

Method C

Synthesis of 5-tert-Butyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid methylamide. (Example 4)



Step 1

A solution of methyl-3-amino-5-t-butylthiophene-2-carboxylate (20.0 g, 93.9 mmol), benzyl chloroformate (80.4 mL, 563 mmol), sodium carbonate (1.10 g, 9.93 mmol), toluene (400 mL) and water (50 mL) was kept at reflux 18 h. Solvent was removed in vacuo and resulting oil dissolved in ethyl acetate, washed with water, brine, dried over magnesium sulfate and concentrated in vacuo affording the corresponding benzyl carbamate ester in quantitative crude yield.

Step 2

The carbamate ester (13.6 g, 39.2 mmol) was dissolved in saturated methyl amine/methanol (200 mL) in a screw top vessel. Sodium cyanide (0.98 g, 20 mmol) was suspended in the solution. The vessel was sealed and heated to 50 °C for 8 h. The solution was poured into water (500 mL) and extracted with ethyl acetate. The ethyl acetate layer was then washed with water, brine, dried over sodium sulfate, and concentrated in vacuo. The crude material was purified by flash chromatography with ethyl acetate/hexane affording 2.76 g (20%) of the N-methyl amide carbamate.

Step 3

The carbamate (2.76 g, 8 mmol) was then dissolved in 100 mL of 1:1 48% hydrobromic acid/ acetic acid and heated to 30 °C for 24 h. The acidic solution was cooled and basidified to pH 4 with saturated sodium bicarbonate. Methyl amine (4 mL, 2 M) in tetrahydrofuran was added before extraction with methylene chloride. Solvent was removed in vacuo affording 922.5 mg (54%) of the N-methyl amide amine.

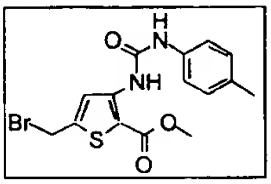
Step 4

A solution of the amine (600 mg, 2.83 mmol), p-tolyl isocyanate (356.4 uL, 2.83 mmol) and 2 mL toluene was heated to reflux for 18 h. Solvent was removed in

vacuo and the resulting solid was purified by flash chromatography with ethyl acetate/ methylene chloride affording 417 mg (44%) of Example 4. ^{1}H NMR ($CDCl_3$) d 10.53 (s, 1h); 7.90 (s,1h); 7.29 (d, 2H, J=8.5Hz); 7.11 (d, 2H, J=8.5Hz); 5.59 (bs, 1h); 2.91 (d, 3H, J=4.9Hz); 2.31 (s,3H);1.38 (s,9H); mp 202-204 °C.

Method D

Synthesis of 5-Bromomethyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid methyl ester. (Example 5)



Step 1

To a dry three-necked flask containing anhydrous methanol (10 mL) kept cold with an ice-water bath was added sodium spheres (116 mg, 5.06 mmol). After the sodium spheres were completely dissolved, methyl thioglycolate (537 mg, 5.06 mmol) was added. After ca. 5 min, a solution of crude 4-(2-tetrahydropyranoxy)-2-butyl-nitrile (0.76 g, 4.60 mmol) [Murray, R.; Zweifel, G., Synthesis, 1980, 150] in methanol (10 mL) was added to the mixture. The mixture was allowed to warm up to rt and maintained at this temperature for 2 h. The mixture was concentrated and the concentrate was partitioned between EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with brine (2 x 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by Chromatotron (4 mm plate, hexane-EtOAc, 9:1) to afford the aminothiophene (593 mg, 48 %) as an orange oil. ^{1}H NMR ($CDCl_3$) d 6.57 (s, 1H); 5.00 (br s, 2H); 4.79-4.72(m, 1H); 4.62 (s, 2H); 3.90-3.80 (m, 1H); 3.82 (s, 3H); 3.58-3.53 (m, 1H); 1.90-1.52 (m, 6H); GC-MS 271 $[M]^+$.

Step 2

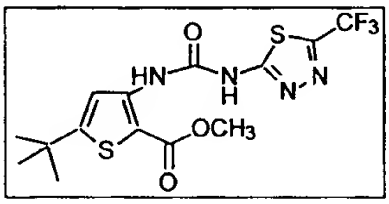
The amine in Step 1 was converted to 5-hydroxymethyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid methyl ester following Method E using toluidine in place of 2-amino-5-trifluoromethyl-1,3,4-thiadiazole. ^{1}H NMR (DMSO-d_6) d 9.86 (s, 1H); 9.48 (s, 1H); 7.83 (s, 1H); 7.34 (d, J = 8.1 Hz, 2H); 7.07 (d, J = 8.5 Hz, 2H); 5.71 (t, J = 5.0 Hz, 1H); 4.61 (d, J = 4.4 Hz, 2H); 3.79 (s, 3H); 2.21 (s, 3H); MS (FAB-LSIMS) 321.2 $[M+H]^+$; mp 166-168 °C.

Step 3

To a solution of 5-hydroxymethyl-3-(3-p-tolyl-ureido)-thiophene-2-carboxylic acid methyl ester (25 mg, 0.078 mmol) in anhydrous DMF (2 mL) was added N-bromosuccinimide (28 mg, 0.156 mmol), and triphenylphosphine (41 mg, 0.156 mmol). The mixture was heated to 50 °C and maintained at this temperature for an hour. The mixture was cooled down to rt. Methanol (0.5 mL) was added to destroy excess reagent. After 10 min, Et_2O (25 mL) was added and the mixture was washed with H_2O (10 mL), saturated $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), and concentrated in vacuo . The crude product was purified by Chromatotron (2 mm plate, 2 % EtOAc in hexane) to afford Example 5 (12.5 mg, 42 %) as a white solid . ^1H NMR ($CDCl_3$) d 9.59 (s, 1H); 8.10 (s, 1H); 7.28 (d, 2H, J = 8.5 Hz); 7.17 (d, 2H, J = 8.1 Hz); 6.70 (bs, 1H); 4.59 (s, 2H); 3.82 (s, OCH_3); 2.34 (s, 3H); MS (FAB-LSIMS) 382, 384 $[M+H]^+$; m.p. 157-158 C.

Method E

Synthesis of 5-tert-Butyl-3-[3-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-ureido]-thiophene-2-carboxylic acid methyl ester. (Example 6)



Step 1

To a solution of 20% phosgene in toluene (37.8 ml, 73.0 mmol) in dichloromethane (90 ml) at -15 °C was slowly added a solution of pyridine (5.9 ml, 73.0 mmol) and methyl 3-amino-5-tert-butyl thiophene-2-carboxylate (10.39 g, 48.7 mmol) in dichloromethane (60 ml). The reaction was allowed to slowly warm to 20 °C over 18 h. The resulting slurry was concentrated in vacuo to dryness and resuspended in ethyl ether and filtered with argon pressure through a glass frit. The solvent was removed in vacuo and the isocyanate residue was diluted to 0.2 M in toluene.

Step 2

A solution of 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (84.5 mg, 500 umol) in 2 ml of the toluene solution from step 1 (400 umol) was stirred for 18 h and the solvent was removed in vacuo. The crude product was purified by flash chromatography with ethyl acetate/hexane affording 144.3 mg (88%) of Example 6 as a foam. ^1H NMR

($CDCl_3$) d 12.5 (bs, 1H); 10.3 (s, 1H); 7.8 (s, 1H); 3.8 (s, 3H); 1.4 (s, 9H). FAB-MS $(M+H)^+$ 409.

5-tert-Butyl-3-[3-(1-methyl-1H-pyrazol-3-yl)-ureido]-thiophene-2-carboxylic acid methyl ester (example 9) was synthesized according to this procedure using N-methyl-3-amino-pyrazole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

5-tert-Butyl-3-[3-(5-tert-butyl-[1,3,4]thiadiazol-2-yl)-ureido]-thiophene-2-carboxylic acid methyl ester (example 10) was synthesized according to this procedure using 2-amino-5-t-butyl-1,3,4-thiadiazole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

5-tert-Butyl-3-[3-(1H-indol-5-yl)-ureido]-thiophene-2-carboxylic acid methyl ester (example 11) was synthesized according to this procedure using 5-amino indole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

5-tert-Butyl-3-[3-(5-methyl-thiazol-2-yl)ureido]-thiophene-2-carboxylic acid methyl ester (example 12) was synthesized according to this procedure using 2-amino-5-methyl thiazole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

5-tert-Butyl-3-[3-(5-ethyl-[1,3,4]thiadiazol-2-yl)ureido]-thiophene-2-carboxylic acid methyl ester (example 13) was synthesized according to this procedure using 2-amino-5-ethyl-1,3,4-thiadiazole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

5-tert-Butyl-3-[3-(5-methyl-[1,3,4]thiadiazol-2-yl)ureido]-thiophene-2-carboxylic acid methyl ester (example 14) was synthesized according to this procedure using 2-amino-5-methyl-1,3,4-thiadiazole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

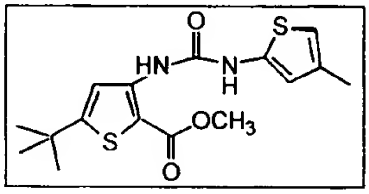
5-tert-Butyl-3-[3-(5-cyclopropyl-[1,3,4]thiadiazol-2-yl)ureido]-thiophene-2-carboxylic acid methyl ester (example 15) was synthesized according to this procedure using 2-amino-5-cyclopropyl-1,3,4-thiadiazole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

5-tert-Butyl-3-{3-[2-(1-methyl-1H-pyrrol-2-yl)-ethyl]ureido}-thiophene-2-carboxylic acid methyl ester (example 16) was synthesized according to this

procedure using 2-(2-aminoethyl)-1-methyl-pyrrole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

Method F

Synthesis of 5-tert-Butyl-3-[3-(4-methyl-thiophen-2-yl)ureido]-thiophene-2-carboxylic acid methyl ester. (Example 17)



Step 1

A solution of 3-methylthiophene (5 ml, 51.75 mmol) and sodium persulfate (18.48 g, 77.6 mmol) and palladium acetate (5.81 g, 25.9 mmol) in acetic acid (500 ml) was heated to reflux. A slow stream of carbon monoxide was bubbled through the solution for 3 h. The reaction was cooled to 20 °C and concentrated in vacuo. The residue was dissolved in dichloromethane, celite was added and the solution was filtered and then passed through a pad of silica gel and concentrated in vacuo. The residue was dissolved in ethyl acetate and extracted into 2 N potassium hydroxide. The aqueous layer was washed with ethyl acetate and the pH was lowered to zero with HCl (conc.). The product was extracted into ethyl acetate, washed with saturated sodium chloride and concentrated in vacuo to yield 1.86 g (25%) of a mixture of 3-methyl-2-thiophene-carboxylic acid and 4-methyl-2-thiophene-carboxylic acid.

Step 2

A solution of 3-methyl-2-thiophene-carboxylic acid and 4-methyl-2-thiophene carboxylic acid (1.11 g, 7.81 mmol) and triethylamine (1.3 ml, 9.38 mmol) in acetone (75 ml) was cooled to -15 °C and ethyl chloroformate (1.12 ml, 11.72 mmol) was slowly added. The mixture was stirred for 15 min and sodium azide (863 mg, 13.28 mmol) in water (15 ml) was added. The reaction was stirred for 30 min, then diluted with dichloromethane and washed with 50% saturated sodium chloride. The organic phase was dried with magnesium sulfate and the solvent was removed in vacuo. The residue was purified by flash chromatography with hexane/ethyl acetate to give 913 mg (70%) of the mixture of azide esters.

Step 3

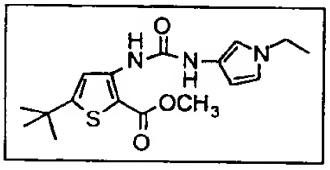
The azide ester (120 mg, 718 umol) was dissolved in toluene (3 ml) and heated to 100 °C for 5 h, then cooled to 20 °C. Methyl 3-amino-5-tert-butyl-2-thiophene carboxylate (106 mg, 500 umol) was added and the reaction was heated to 95 °C for 18 h. The reaction was cooled to 20 °C and the solvent was removed in vacuo. The crude material was purified by flash chromatography with hexane/ethyl acetate and then purified by normal phase HPLC with dichloromethane, affording 82.1 mg (46%) of Example 17 and 18 mg (10%) of 3-methyl-thiophene derivative.

5-tert-Butyl-3-(3-thiophen-2-yl-ureido)-thiophene-2-carboxylic acid methyl ester (example 7) was synthesized according to this procedure steps 2 and 3 using 2-thiophene carboxylic acid in place of 3-methyl-2-thiophene-carboxylic acid.

5-tert-Butyl-3-[3-(5-methyl-thiophen-2-yl)ureido]-thiophene-2-carboxylic acid methyl ester (example 8) was synthesized according to this procedure steps 2 and 3 using 5-methyl-2-thiophene carboxylic acid in place of 3-methyl-2-thiophene-carboxylic acid.

Method G

Synthesis of 5-tert-Butyl-3-[3-(1-ethyl-1H-pyrrol-3-yl)-ureido]-thiophene-2-carboxylic acid methyl ester. (Example 18)



Step 1

A solution of 3-nitropyrrole (446 mg, 4.16 mmol), cesium carbonate (1.63 g, 4.99 mmol), iodoethane (998 ul, 12.48 mmol) in DMF (10 ml) was stirred for 2.5 hours at 20 °C. The reaction was diluted with ethyl acetate, washed 1N hydrochloric acid (3x), dried with sodium sulfate and the solvent removed in vacuo. The crude material was purified by flash chromatography with 100% dichloromethane affording 480 mg (82%) as an oil.

Step 2

To a solution of the product from Step 1 (480 mg, 3.43 mmol) in methanol (10 ml) was added 10% palladium on charcoal (30 mg). The reaction was hydrogenated at

atmospheric pressure for 18 h at 20 °C, then filtered. The solvent was removed in vacuo affording 342 mg (91%) as a oil.

Step 3

A solution of the product from Step 2 (342 mg, 3.11 mmol) and methyl-5-t-butyl-3-isocyanothiophene-2-carboxylate (0.2 M in toluene, 3 ml) was stirred for 20 h at 20 °C. The solvent was removed in vacuo and the crude material was purified by flash chromatography with ethyl acetate/hexane affording 136 mg (65%) of Example 18 as a foam. ^{1}H NMR ($CDCl_3$) d 9.7 (s, 1H); 8.0 (s, 1H); 7.75 (s, 1H); 7.65 (m, 2H); 7.3 (m, 2H); 3.8 (s, 3H); 1.3 (s, 9H). FAB-MS $(M+H)^+$ 350.

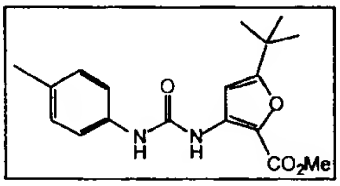
5-tert-Butyl-3-[3-(1-propyl-1H-pyrrol-3-yl)-ureido]-thiophene-2-carboxylic acid methyl ester (example 19) was synthesized according to this procedure using allyl bromide in place of the iodoethane.

5-tert-Butyl-3-[3-(1-isopropyl-1H-pyrrol-3-yl)-ureido]-thiophene-2-carboxylic acid methyl ester (example 20) was synthesized according to this procedure using 2-bromopropane in place of the iodoethane.

5-tert-Butyl-3-[3-(1-ethyl-1H-pyrazol-3-yl)-ureido]-thiophene-2-carboxylic acid methyl ester (example 21) was synthesized according to this procedure using 3-nitropyrazole in place of the 3-nitropyrrole.

Method H

Synthesis of 5-tert-Butyl-3-(3-p-tolyl-ureido)-furan-2-carboxylic acid methyl ester. (Example 22)



Step 1

n-Butyllithium (25 mL, 40 mmol, 1.6 M in hexane solution, 1.1 equiv) is added dropwise to a solution of 4.5 g of 2-t-butylfuran (36 mmol) in 60 mL of dry THF at -78 °C under N_2. After 30 min, the cooling bath is replaced with an ice bath and the mixture stirred at 0 °C for 1 h. Dry CO_2, generated from dry ice and dried over an anhydrous Na_2SO_4 tower, is bubbled into the reaction mixture over 20 min at -78 °C

and then at 0 °C. The reaction mixture is acidified with 1 M HCl to pH 1, then extracted with ethyl acetate. The organic layer is washed with brine, dried ($NaSO_4$) and concentrated to give 4.2 g of 2-tertbutyl 5-furanoic acid as a pale yellow solid (69%). ^{1}H NMR ($CDCl_3$) d 11.0 (br s, 1H), 7.19 (d, 1H, J = 3.3 Hz), 6.11 (d 1H, J = 3.3 Hz), 1.29 (s, 9H).

Step 2

A solution of 2.0 g of the furanoic acid (11.9 mmol) in 30 mL of dry THF is cooled to -78 °C under N_2 before the dropwise addition of 15.6 mL of n-butyllithium (25 mmol, 1.6 M in hexane solution, 2.1 equiv). After 30 min, 2.3 g of TsN_3 (11.9 mmol, 1.1 equiv) in 3 mL of dry THF (3 mL wash) is added dropwise via cannula. The yellow solution is allowed to heat to 0 °C over 2 h, then 6 g of potassium acetate (60 mmol, 5 equiv) is added and the suspension is stirred rapidly at rt for 14 h. The mixture is diluted with ether and extracted with water. The aqueous phase is acidified to pH 1 with 1 M HCl, then extracted thoroughly with ethyl acetate. The organic phase is washed further with brine, dried over $NaSO_4$ and concentrated. A hexane solution of $TMSCHN_2$ (45 mL, 90 mmol, 2.0 M) is added to the red oil in 150 mL of ether and 20 mL of methanol. After 30 min, the mixture is concentrated, and subjected to flash chromatography (10% ethyl acetate in hexane) to give 1.72 g of a colorless oil. Analysis of the product by ^{1}HNMR indicates a ~2:3 mixture of the title compound and 5-t-butyl-2-furanoic acid methyl ester, which co-elute. The mixture is used without further purification. FTIR (film) cm^{-1} 2965 (s), 2118 (s), 1723 (s); ^{1}H NMR ($CDCl_3$) d 5.99 (s, 1H), 3.80 (s, 3H), 1.25 (s, 9H).

Step 3

A Parr bottle containing 1.72 g of the mixture obtained from the above reaction and 0.5 g of Pd (10% on carbon) in 30 mL of cellosolve is successively evacuated and purged with H_2 gas three times. The reaction mixture is then shaken under an atmosphere of H_2 (40 psi) for 1 h, diluted with ethyl acetate and filtered through celite. The concentrated solution is flash chromatographed (20% ethyl acetate in hexane) to give 0.59 g of the amine (25% total yield) as a crystalline solid as well as 0.73 g of recovered methyl ester (34%). FTIR (film) cm^{-1} 3330-2950 (s, br), 2850 (m), 1680 (s), 1637 (s), 1537 (s), 1346 (s), 1131 (s); ^{1}H NMR ($CDCl_3$) d 5.76 (s, 1H), 4.24 (br s, 2H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$) d 178.7, 168.1, 160.5, 144.9 (br), 124.1, 98.3, 50.5, 32.8, 28.3.

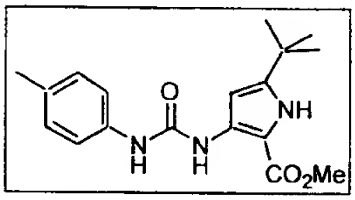
Step 4

Phosgene (1.3 mL, 2.5 mmol, 1.93 M solution in toluene, 10 equiv) is added rapidly to a solution of 50 mg of the product from step 3 (0.25 mmol) in 1.0 mL of dry pyridine and 5 mL of dry toluene at rt under N_2. After 30 min, the orange suspension is concentrated in vacuo, then successively charged with 1 mL of dry toluene and evaporated (2 times). Finally, 3 mL of toluene is added before the addition of 100 mg of toluidine (0.93 mmol, 3.7 equiv). The orange mixture is stirred overnight, diluted with ethyl acetate and washed with 1 M HCl, and brine, then dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography to give 80 mg of Example 22 (96%) as a pale yellow oil. FTIR (film) cm^{-1} 3400-3200 (m, br), 2966 (s), 1676 (s), 1622 (s), 1536 (s), 1306 (s), 1097 (m); ^1H NMR ($CDCl_3$) d 8.68 (br s, 1H), 7.87 (br s, 1H), 7.27 (d, 2H, J = 8.1 Hz), 7.11 (d, 2H, J = 8.1 Hz), 7.02 (s, 1H), 3.77 (s, 3H), 2.30 (s, 3H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$) d 168.2, 160.5, 152.5, 137.7, 134.8, 134.0, 129.5, 126.0, 121.4, 100.1, 51.0, 33.0, 28.3, 20.6.

5-tert-Butyl-3-[3-(3,4-dichloro-phenyl)-ureido]-furan-2-carboxylic acid methyl ester (example 23) was synthesized according to this procedure using amino-3,4-dichlorobenzene in place of the toluidine.

Method I

Synthesis of 5-tert-Butyl-3-(3-p-tolyl-ureido)-1H-pyrrole-2-carboxylic acid methyl ester. (Example 24)



Step 1

Chlorotrimethylsilane (17.9 mL, 141 mmol, 2.5 equiv) is added in one portion to a solution of pyrrole-2-carboxylic acid (6.28 g, 56.5 mmol) in dry methanol (100 mL) under N_2 at rt. After stirring overnight, the reaction mixture is concentrated in vacuo, redissolved in dichloromethane, washed with water, dried (Na_2SO_4) and concentrated to give 4.62 g of methyl pyrrole-2-carboxylate as a tannish semi-crystalline solid (65%), which was used without further purification. ^1H NMR ($CDCl_3$) d 9.3 (br s, 1H), 6.96 (br m, 1H), 6.92 (br m, 1H), 6.29 (br q, 1H), 3.86 (s, 3H).

Step 2

Aluminum chloride (0.710 g, 5.33 mmol, 2.2 equiv) is added in one portion to a solution of methyl pyrrole-2-carboxylate (0.30 g, 2.42 mmol) in dry dichloroethane (12 mL) under N_2 at rt. Subsequently, 2-chloro-2-methylpropane (0.26 mL, 2.42 mmol, 1.0 equiv) is added in one portion via syringe. After 2 h, the orange solution is quenched by slowly pouring into a saturated sodium bicarbonate solution. The resulting white suspension is extracted with diethyl ether (2 x). The combined organic layers are dried (Na_2SO_4) and concentrated in vacuo to give 0.40 g of methyl 5-t-butylpyrrole-2-carboxylate as an off-white solid. Flash chromatography (40% hexane in dichloromethane) gives 0.3 6 g of the desired material as a white amorphous solid (81%). ^{1}H NMR ($CDCl_3$) d 8.82 (br s, 1H), 6.81 (t, 1H, J = 3.3 Hz), 6.00 (t, 1H, J = 3.3 Hz), 3.83 (s, 3H), 1.31 (s, 9H).

Step 3

Fuming nitric acid (0.57 mL, 13.6 mmol, 1.5 equiv) is added in one portion via syringe to a heterogeneous mixture of methyl-5-t-butylpyrrole-2-carboxylate (1.65 g, 9.10 mmol) in concentrated sulfuric acid (19 mL) under N_2 at rt. After 1 h, the reaction is poured over ice-water and slowly neutralized to pH 7 with solid sodium carbonate, extracted with diethyl ether (2 x), dried (Na_2SO_4), and concentrated in vacuo. The residue is subjected to flash chromatography (30% hexane in dichloromethane) to give 0.44 g of the desired product, in addition to 0.27 g of bis-nitrated product which has higher mobility. Rechromatographing of mixed fractions provides a further 0.22 g of methyl 5-t-butyl-3-nitropyrrole-2-carboxylate (32 % total yield). Mono-nitrated: ^{1}H NMR ($CDCl_3$) d 9.22 (br s, 1H), 6.56 (d, 1H, J = 3.3 Hz), 3.93 (s, 3H), 1.33 (s, 9H). Bis-nitrated: ^{1}H NMR ($CDCl_3$) d 9.17 (br s, 1H), 3.91 (s, 3H), 1.52 (s, 9H).

Path A

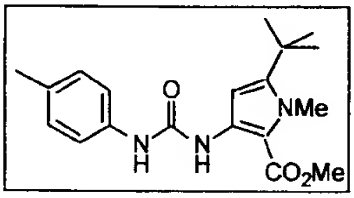
Step 4

A Parr hydrogenation bottle fitted with a 16 x 100 mm disposable glass culture tube is charged with methyl-5-t-butyl-3-nitropyrrole-2-carboxylate (14 mg, 0.062 mmol) in dry methanol (1 mL) and Pd (10% on carbon, 3 mg). The reaction is successively evacuated and purged with H_2 gas three times. The reaction mixture is then shaken under an atmosphere of H_2 (35 psi) for 1 h, diluted with dichloromethane and filtered through celite. The filtrate is concentrated in vacuo to give methyl 3-amino-5-t-butylpyrrole-2-carboxylate as a bright yellow oil (100%, crude yield). ^{1}H NMR ($CDCl_3$) d 7.89 (br s, 2H), 5.52 (d, 1H, J = 2.8 Hz), 3.82 (s, 3H), 1.26 (s, 9H).

Step 5

Phosgene (0.32 mL, 0.62 mmol, 1.93 M solution in toluene, 10 equiv) is added rapidly to a solution of methyl-3-amino-5-t-butylpyrrole-2-carboxylate (12.2 mg, 0.062 mmol) and dry pyridine (247 mL, 3.06 mmol, 49.4 equiv) in dry toluene (1 mL). After 30 min, the orange suspension is concentrated in vacuo, then successively charged with 1 mL of dry toluene and evaporated (2 x). Finally, toluene (2 mL) is added before the addition of p-toluidine (10 mg, 0.094 mmol). The mixture is heated at for 3 h before being concentrated in vacuo. The residue is purified by preparative TLC (2 plates, 0.25 mm thick, 20 x 20 cm, 2% methanol in dichloromethane). The major UV active band is isolated and the product is extracted with 5% methanol in dichloromethane to give 16.4 mg of Example 24 as a pale yellow amorphous solid (80%). FT-IR (KBr pellet) cm^{-1} 3341 (s), 2947 (m), 1676 (s), 1583 (s), 1548 (s), 1456 (s), 1279 (s), 1208 (s), 1094 (s); MS (ES) = 330.1 (m+1); ^1H NMR (MeOD, $CDCl_3$) d 8.45 (br s, 1H), 8.19 (br s, 1H), 7.27 (d, 2H, J = 7.3 Hz), 7.14 (d, 2H, J = 8.4 Hz), 6.95 (br s, 1H), 6.78 (d, 1H, J = 2.8 Hz), 3.73 (s, 3H), 2.32 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (MeOD, $CDCl_3$) d 161.89, 153.51, 147.62,136.15, 132.17, 128.90, 119.58, 105.92, 97.36, 50.00, 31.45, 28.99, 19.65.

Synthesis of 5-tert-Butyl-1-methyl-3-(3-p-tolyl-ureido)-1H-pyrrole-2-carboxylic acid methyl ester. (Example 25)



Path B

Step 6

Sodium hydroxide (0.21 g, 2.65 mmol, 50% aqueous, 6 equiv) is added to a cold (0 – -10 °C) solution of methyl 5-t-butyl-3-nitropyrrole-2-carboxylate (100 mg, 0.44 mmol), benzyltributyl ammonium bromide (158 mg, 0.44 mmol, 1 equiv), and dimethyl sulfate (46 mL, 0.49 mmol, 1.1 equiv) in dichloromethane (1 mL). After 5 min, the cooling bath is removed and the mixture is stirred for 4 h at rt. The reaction mixture is diluted with dichloromethane, washed with water (1 x), 10 % ammonium acetate (2 x), dried (Na_2SO_4), and concentrated in vacuo to give a bright yellow oil. The residue is purified by flash chromatography (30% hexane in dichloromethane) to give 61 mg of methyl 5-t-butyl-1-methyl-3-nitropyrrole-2-carboxylate as a pale

yellow oil which solidifies upon standing (62%). ^{1}H NMR ($CDCl_3$) d 6.47 (s, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 1.38 (s, 9H).

Step 7

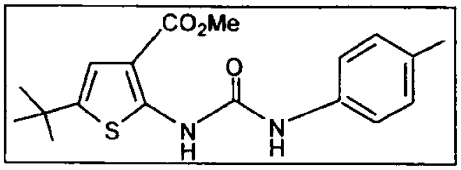
The nitro compound is reduced in a similar manner to that for methyl 3-amino-5-t-butylpyrrole-2-carboxylate to give 59 mg of methyl 3-amino-1-methyl-5-t-butylpyrrole-2-carboxylate as an oil (100%, crude yield). ^{1}H NMR ($CDCl_3$) d 5.48 (s, 1H), 4.34 (br s, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$) d 162.24, 148.95, 142.27, 107.39, 95.73, 50.55, 50.04, 34.73, 31.92, 29.67.

Step 5

Phosgene (1.45 mL, 2.80 mmol, 1.93 M solution in toluene, 10 equiv) is added rapidly to a solution of methyl-3-amino-1-methyl-5-t-butylpyrrole-2-carboxylate (59 mg, 0.280 mmol) in dry pyridine (1 mL) and dry toluene (2 mL). Additional dry toluene (3 mL) is added to aid stirring of the heterogeneous mixture. After 30 min, the orange suspension is concentrated in vacuo, then successively charged with dry toluene (1 mL) and evaporated (2 x). Finally, toluene (3 mL) is added before the addition of p-toluidine (111 mg, 1.04 mmol, 3.7 equiv). The resulting homogeneous mixture is stirred overnight, diluted with dichloromethane and washed with 1 M HCl. The aqueous layer was thoroughly back-extracted with dichloromethane (2 x) and the combined organic phases are dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (10% Æ 25% ethyl acetate in hexane) to give 66 mg of the Example 25 as a pale yellow solid (69%). FT-IR (KBr pellet) cm^{-1} 2364 (s), 2335 (s), 1659 (m), 1579 (m), 1542 (m), 1354 (w), 1232 (w); ^{1}H NMR ($CDCl_3$) d 8.81 (br s, 1H), 7.26 (ap d, 3H (2H + 1 NH), J = 8.4 Hz), 7.11 (d, 2H, J = 8.4 Hz), 6.80 (s, 1H), 3.88 (s, 3H), 3.64 (s, 3H), 2.31 (s, 3H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$) d 161.95, 153.01, 148.59, 135.34, 133.97, 133.78, 129.54, 122.02, 108.82, 98.76, 50.38, 35.03, 32.12, 31.37, 29.76.

Method J

Synthesis of 5-tert-Butyl-2-(3-p-tolyl-ureido)-thiophene-3-carboxylic acid methyl ester. (Example 26)



Step 1

Triethyl amine (3.04 mL, 21.8 mmol) was added to a solution of methyl cyanoacetate (4.00 g, 40.4 mmol), sulfur (1.29 g, 40.4 mmol) and DMF (20 mL) at ambient temperature. 3,3-dimethyl butraldehyde (5.08 g, 40.4 mmol) was added and stirred 1 h before being poured into water (200 mL). Solids were filtered off and filtrate was extracted with ethyl acetate. The acetate layer was filtered through a plug of silica gel and concentrated in vacuo. Purification via flash chromatography afforded 4.19 g (49%) of methyl 2-amino-5-t-butylthiophene 3-carboxylate.

Step 2

Methyl 2-amino-5-t-butylthiophene 3-carboxylate was then condensed with p-tolyl isocyanate under conditions described in Method A, Step 2 to produce 29 mg of Example 26 (18%). ^{1}H NMR ($CDCl_3$) d 10.37 (s, 1h); 7.32 (d, J=8.5 Hz, 2H); 7.16 (d, J=8.1Hz, 2H); 6.82 (s, 1H); 6.75 (bs, 1h); 3.81 (s, 3H); 2.34 (s, 3H);1.38 (s, 9H); mp 109-111 °C.

5-tert-Butyl-2-(3-phenyl-ureido)-thiophene-3-carboxylic acid methyl ester (example 27) was synthesized according to this method using phenyl isocyanate in place of the p-tolyl isocyanate.

5-tert-Butyl-2-(3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-ureido)-thiophene-3-carboxylic acid methyl ester (example 28) was synthesized according to this method step 1 then Method E using 2-amino-5-ethyl-1,3,4-thiadiazole in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

5-Isopropyl-2-(3-p-tolyl-ureido)-thiophene-3-carboxylic acid methyl ester (example 29) was synthesized according to this method step 1 using 3-methyl butraldehyde in place of 3,3-dimethyl butraldehyde followed by Method E using toluidine in place of the 2-amino-5-trifluoromethyl-1,3,4-thiadiazole.

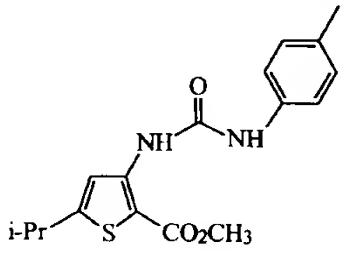
5-Isopropyl-2-[3-(5-methyl-thiophen-2-yl)-ureido]-thiophene-3-carboxylic acid methyl ester (example 30) was synthesized according to this method step 1 using 3-methyl butraldehyde in place of 3,3-dimethyl butraldehyde followed by Method F steps 2 and 3 using 5-methyl-2-thiophene carboxylic acid in place of 3-methyl-2-thiophene-carboxylic acid.

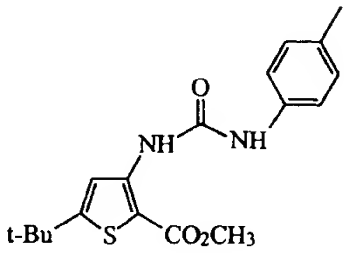
The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

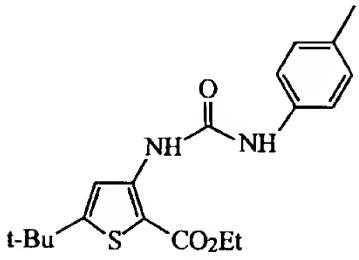
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

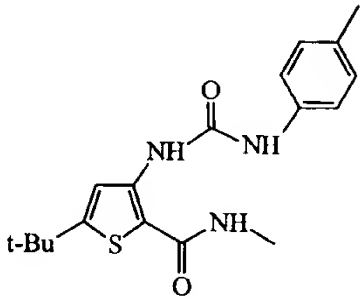
WHAT IS CLAIMED IS:

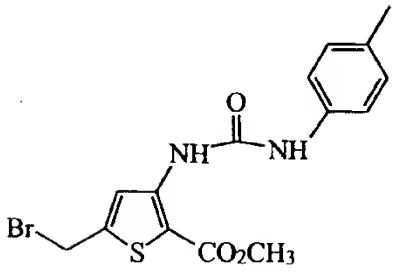
1. A method for the treatment of cancerous cell growth mediated by raf kinase, comprising administering a compound of the formulae:

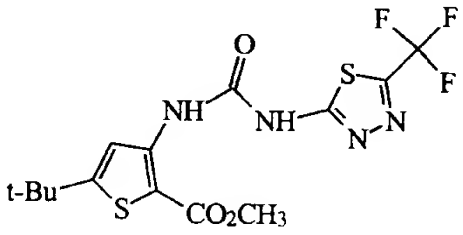


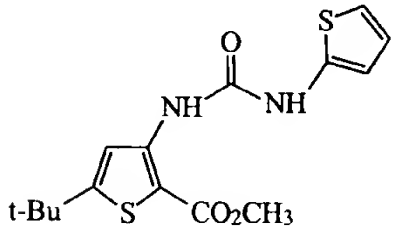


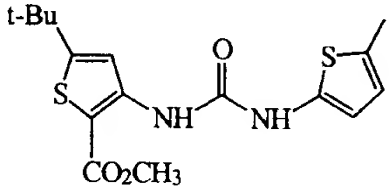


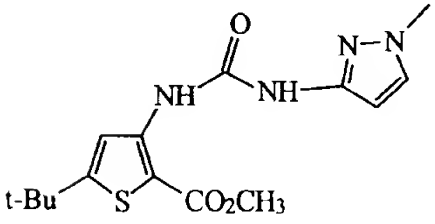


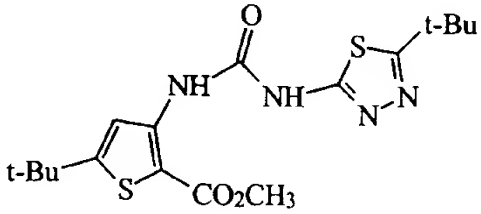


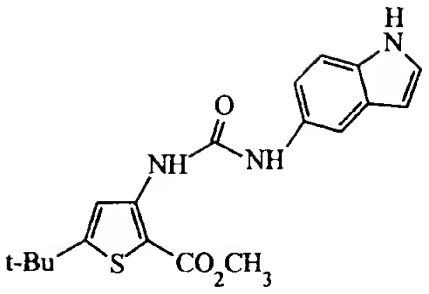


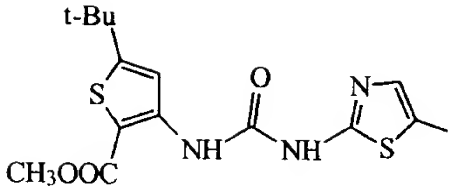


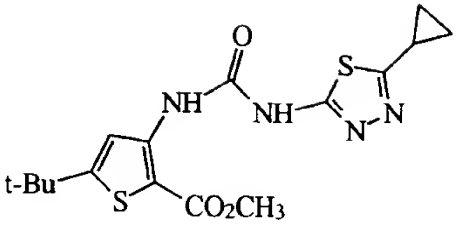


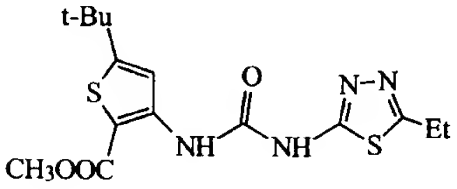


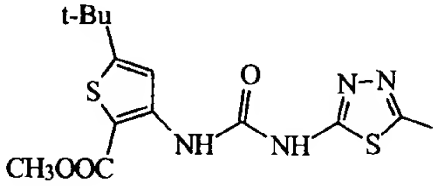


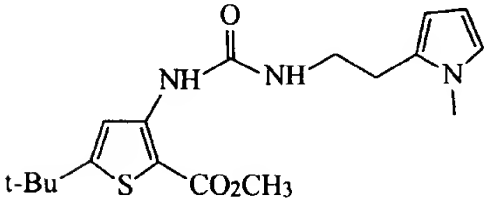


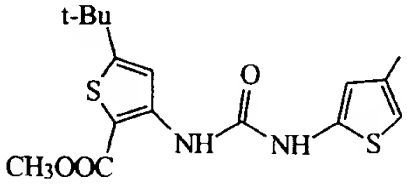


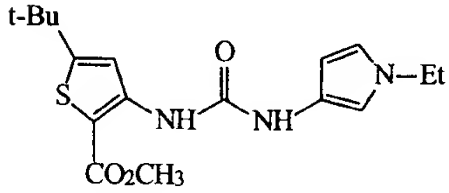


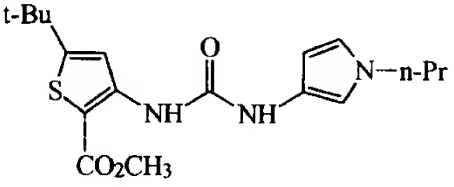


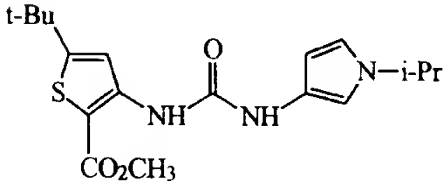


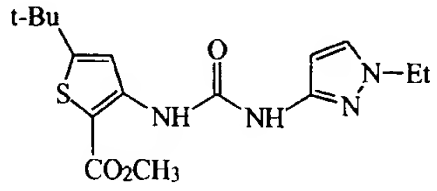












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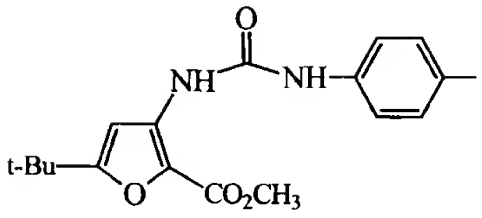

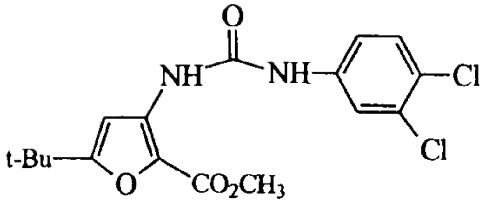

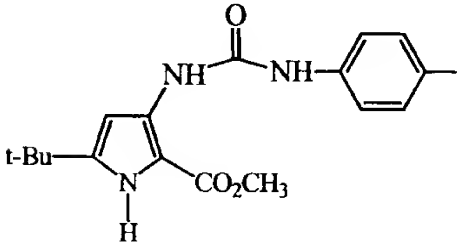

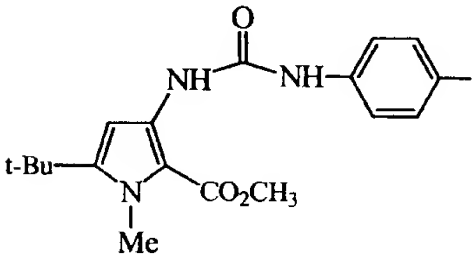

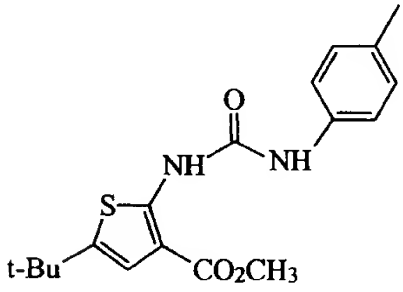

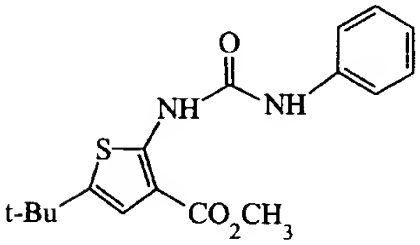

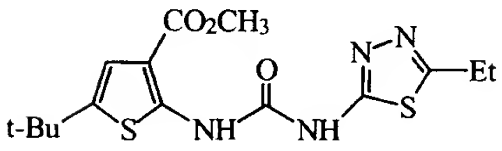

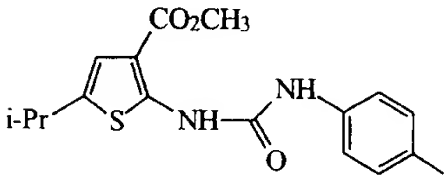

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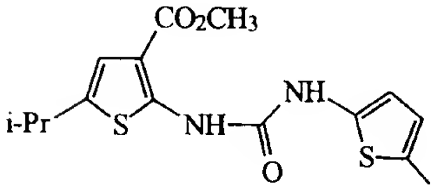
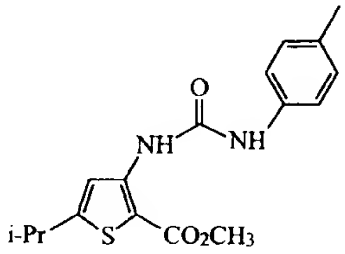
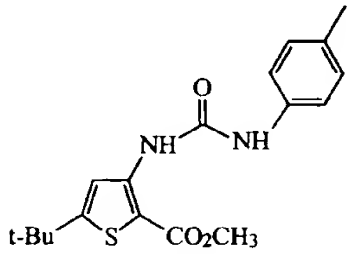
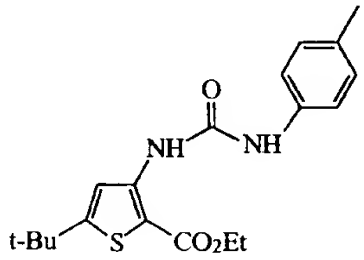
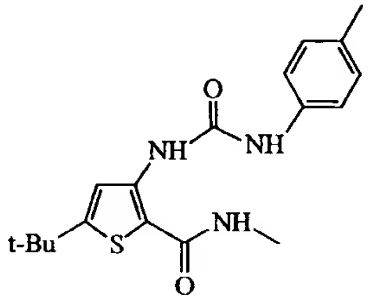


2. A method according to claim 1, comprising administering a compound of the formulae









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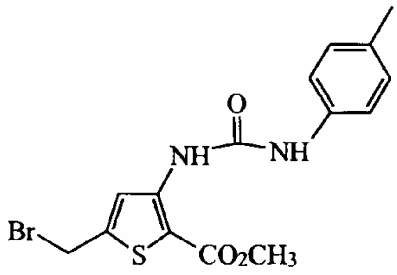

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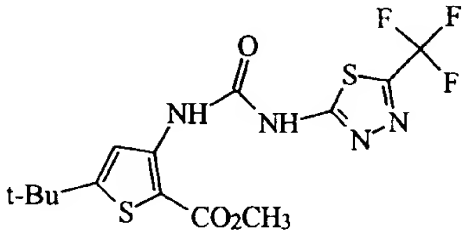
3. A method according to claim 1, comprising administering a compound of the formulae



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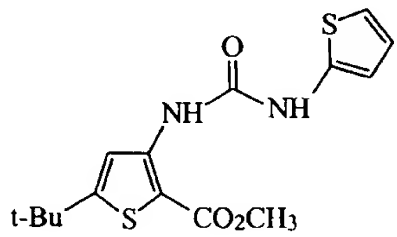

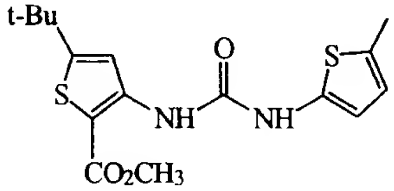

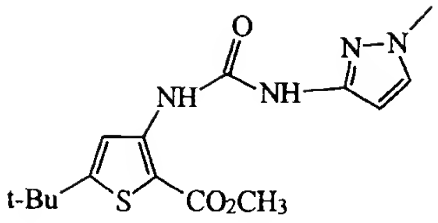

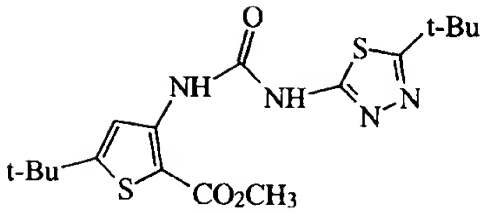

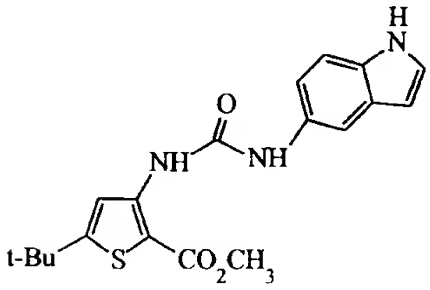

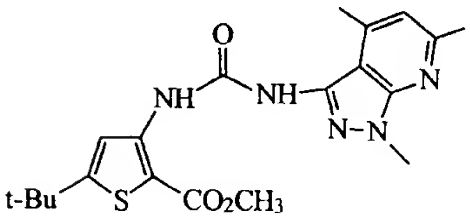

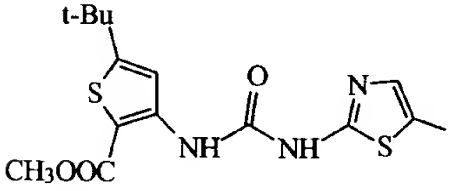

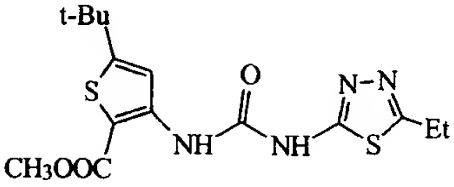

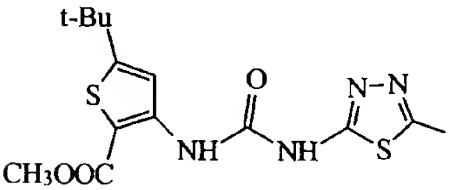

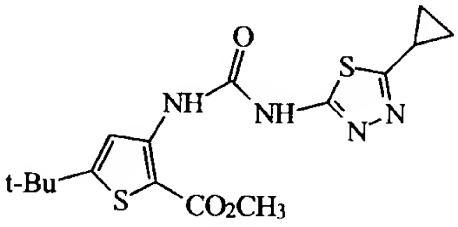

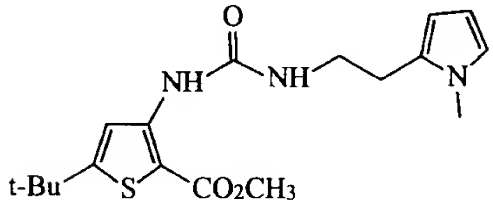

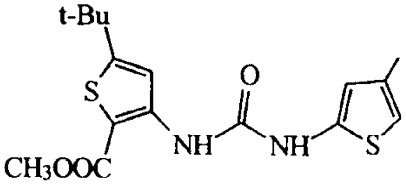

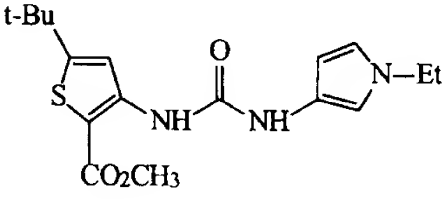

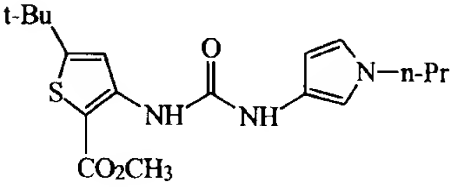

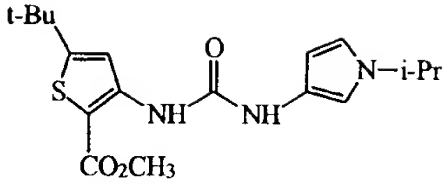

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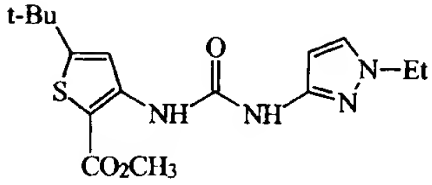
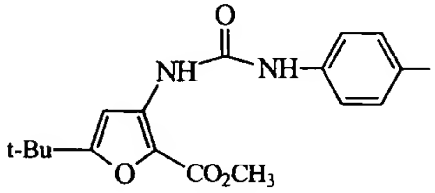


4. A method according to claim 1, comprising administering a compound of formulae



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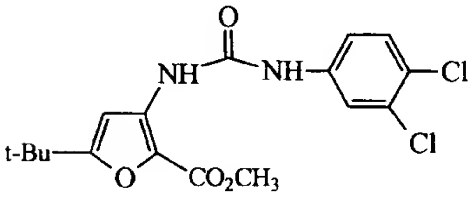
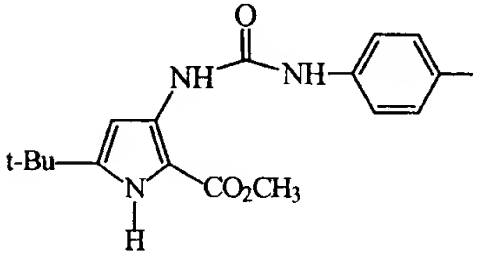


5. A method according to claim 1, comprising administering a compound of formulae



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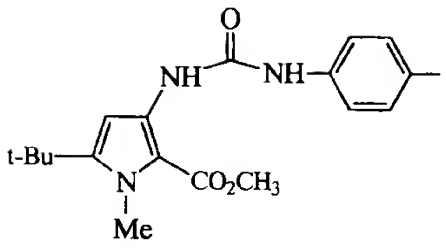
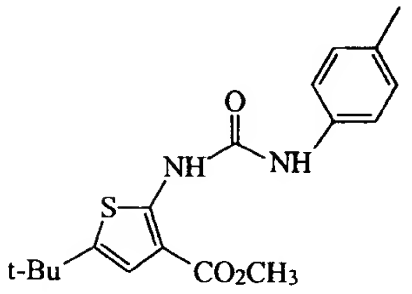
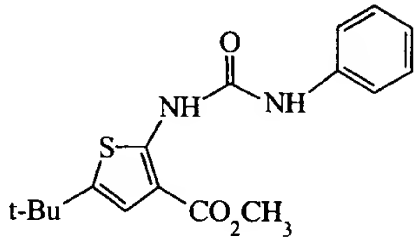
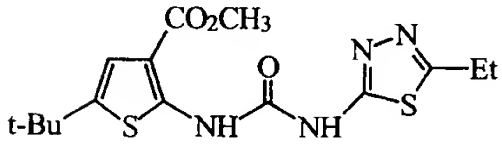
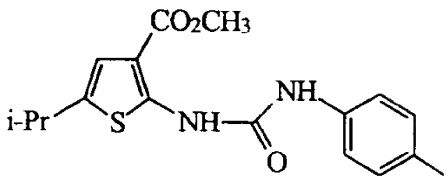


6. A method according to claim 1, comprising administering a compound of formulae









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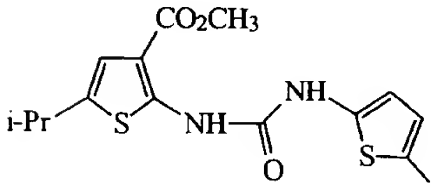
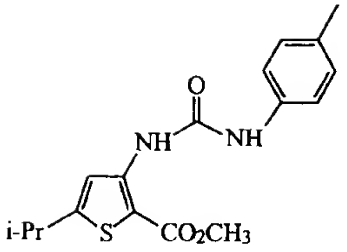
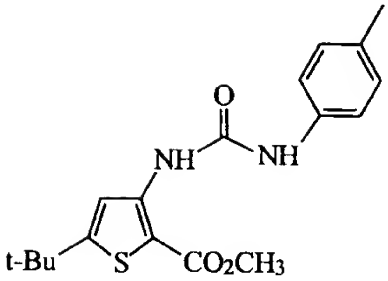
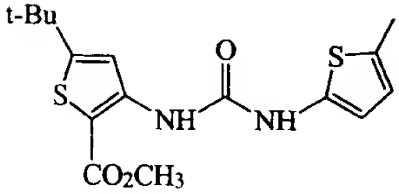
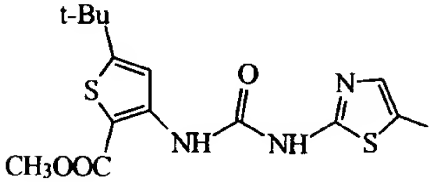


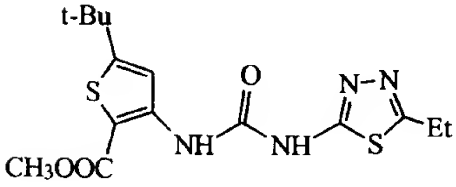
7. A method according to claim 1, comprising administering a compound of formulae

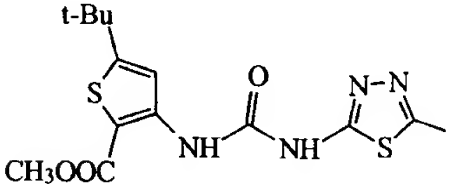


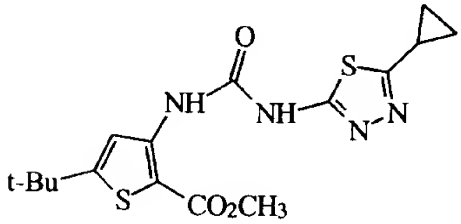


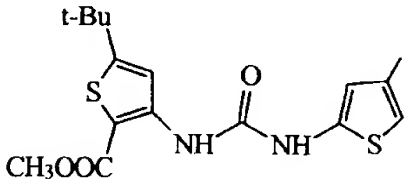


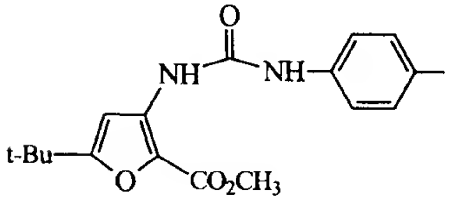


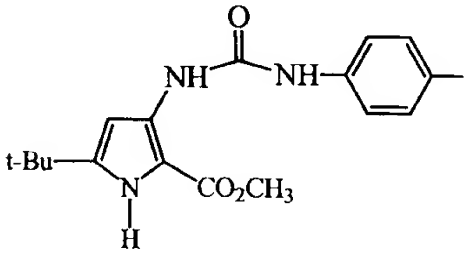


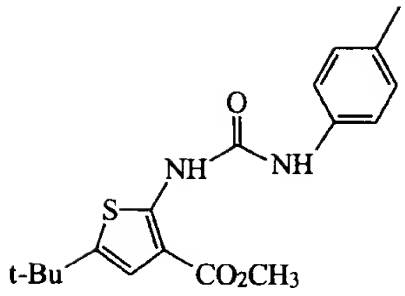












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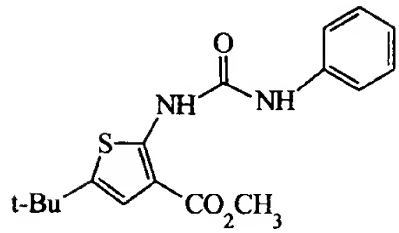
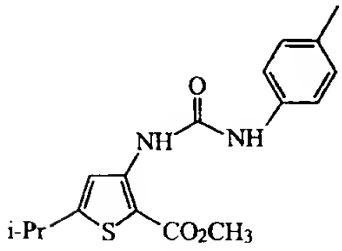
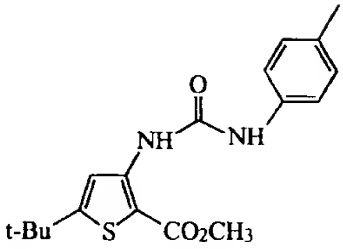
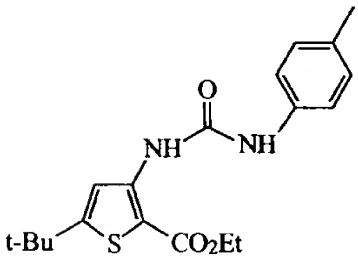
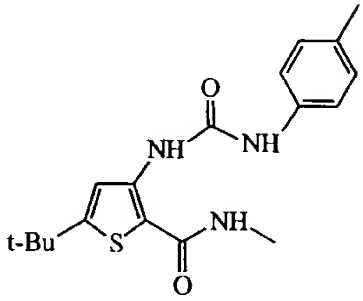


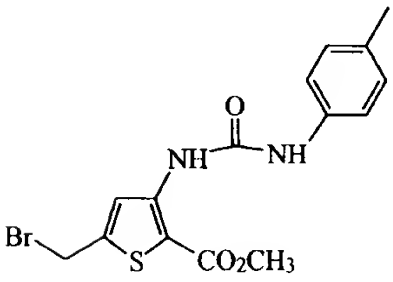
8. A compound of the formulae

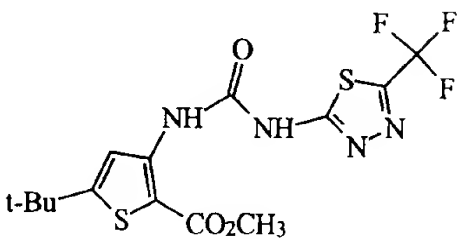


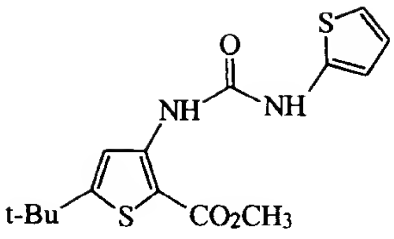


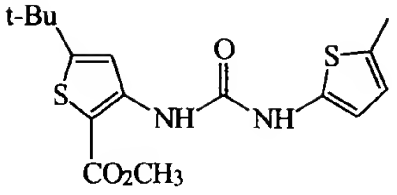


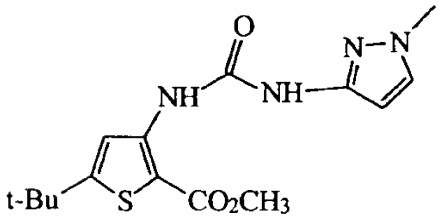


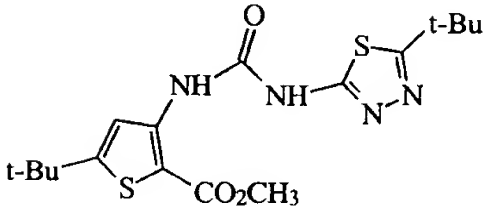


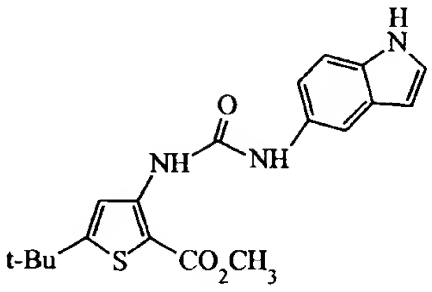


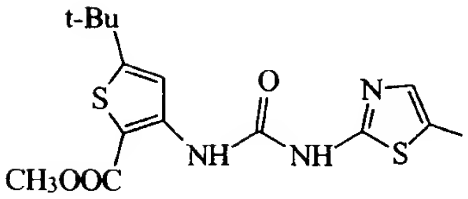


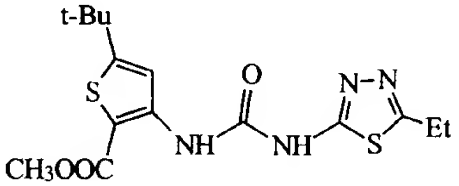


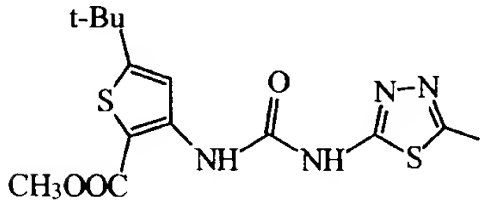


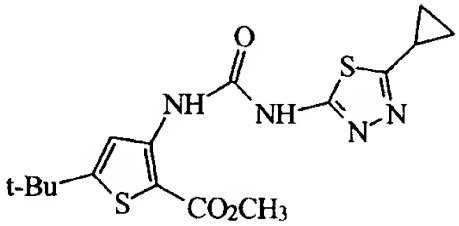


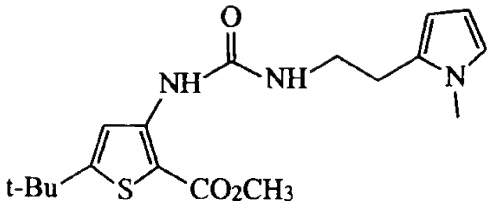


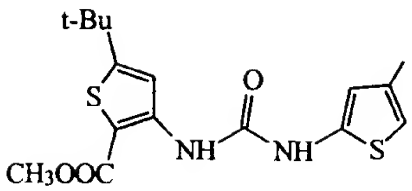


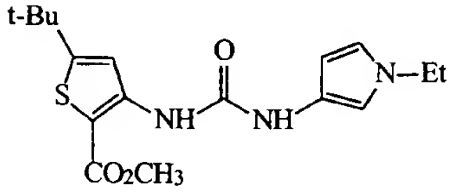


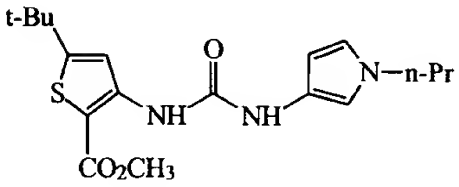


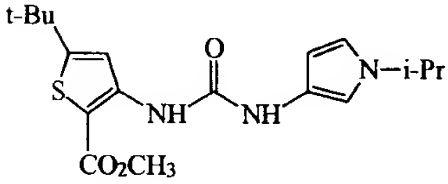


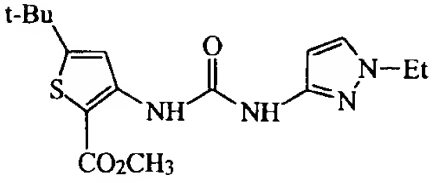


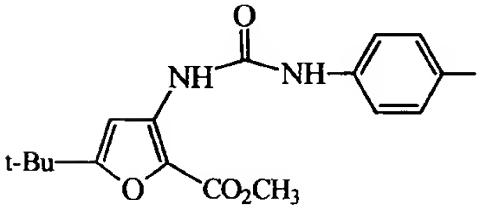


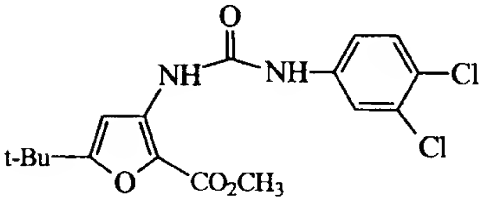


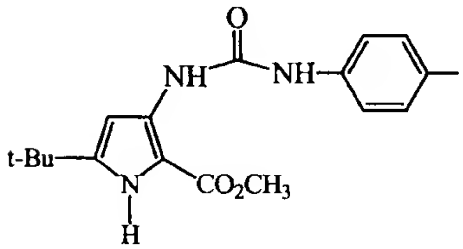


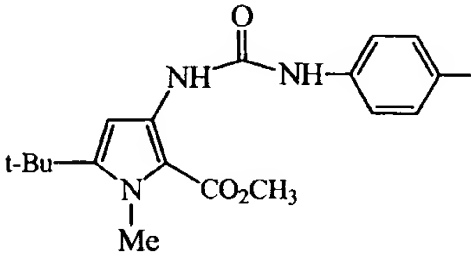


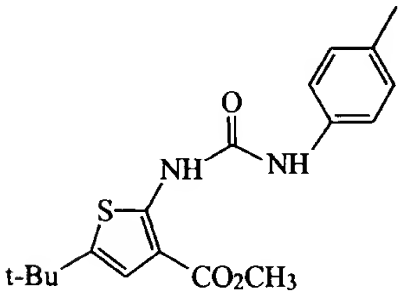


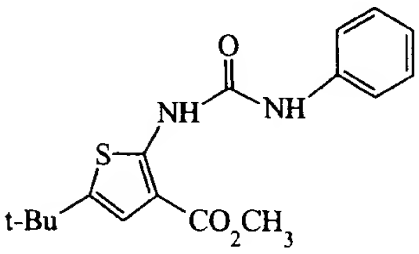


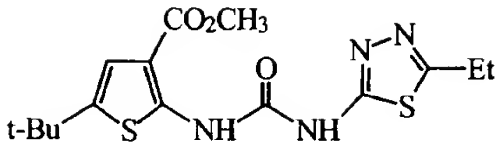


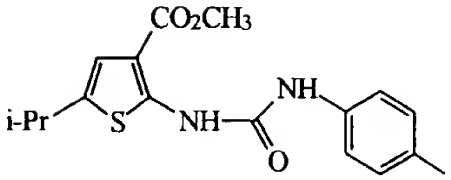












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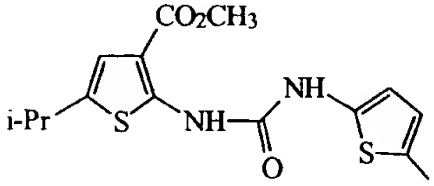
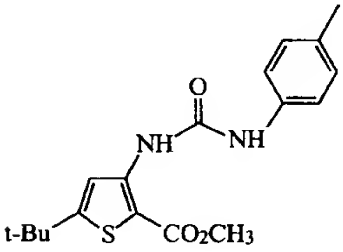
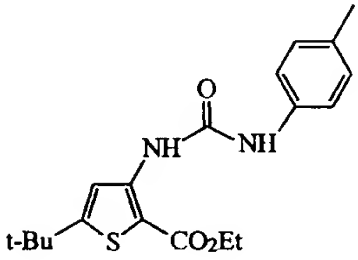
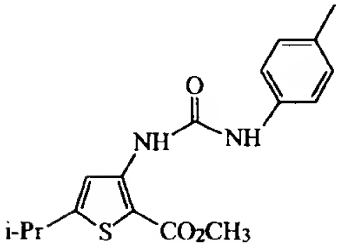
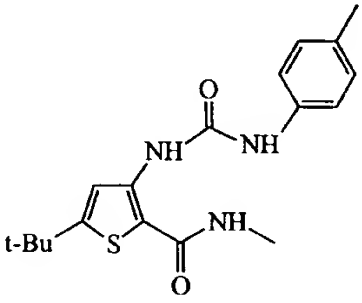


9. A compound according to claim 8, of the formulae









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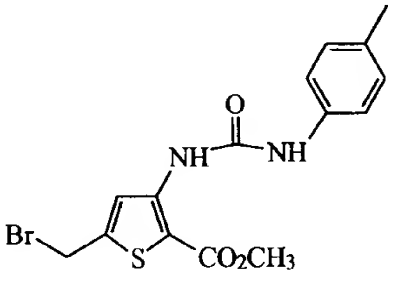
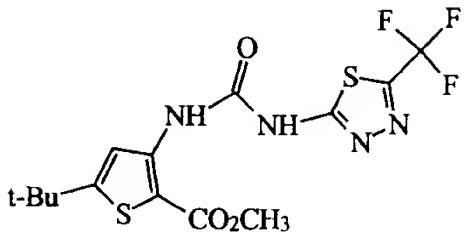
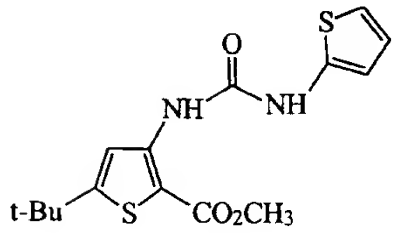
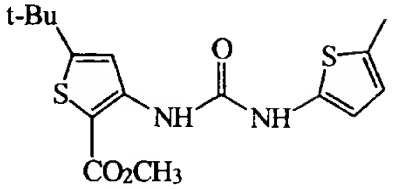
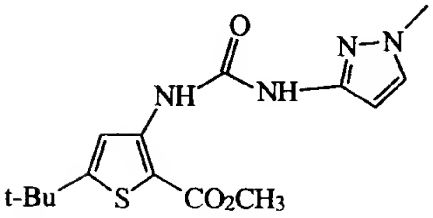


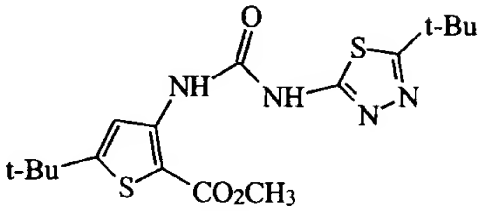
10. A compound according to claim 8, of the formulae

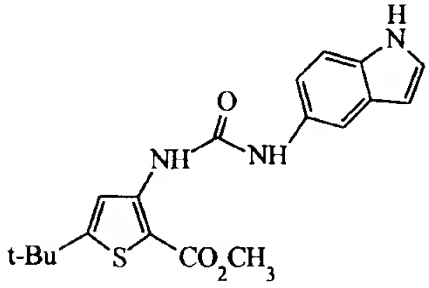


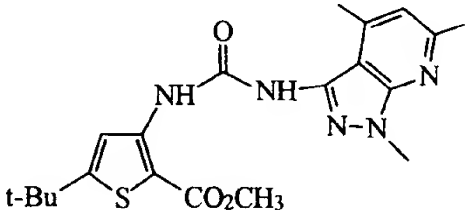


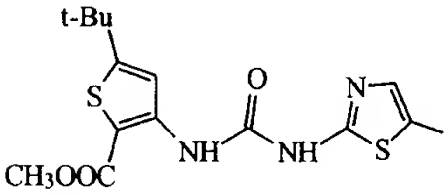


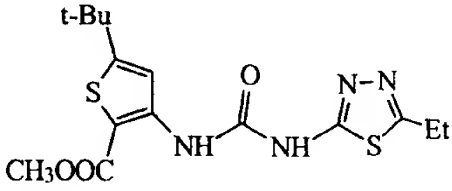


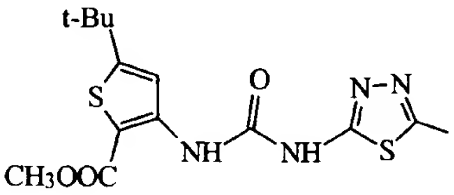


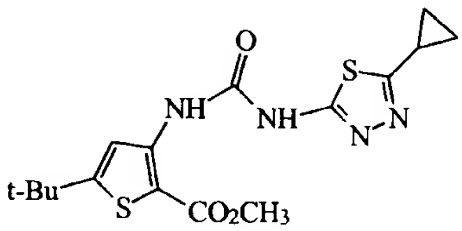


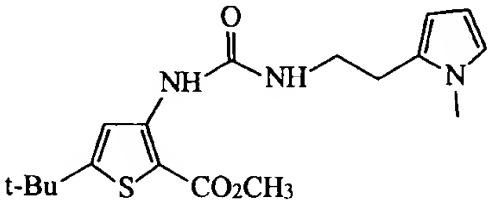


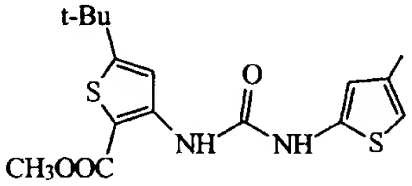


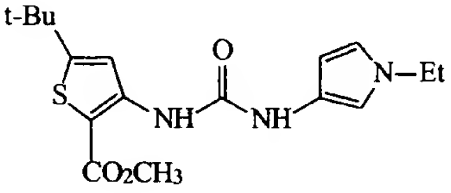


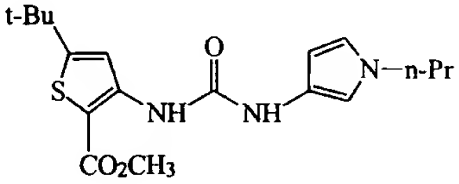


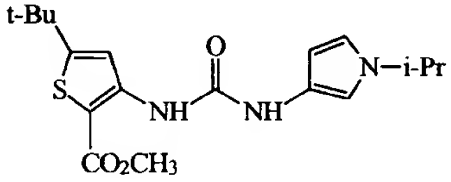












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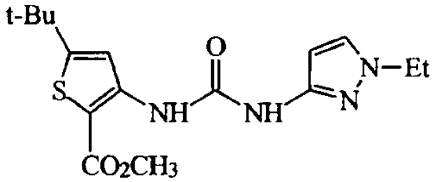
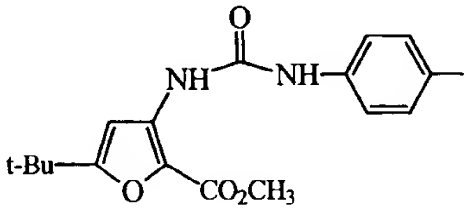


10

11. A compound according to claim 8, of the formulae



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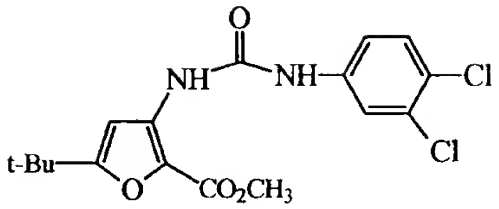
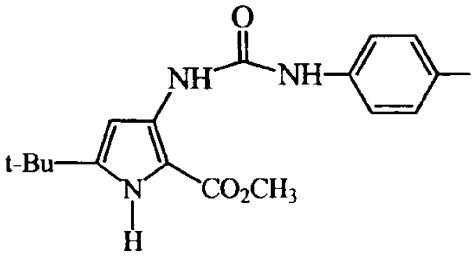


12. A compound according to claim 8, of the formulae



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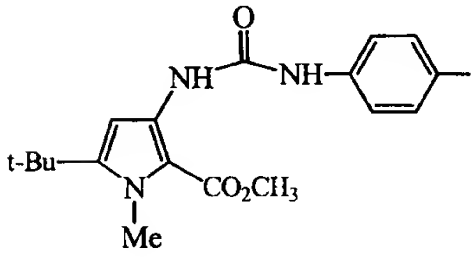
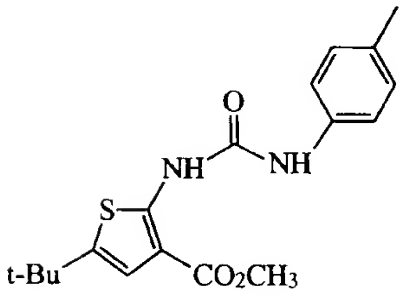
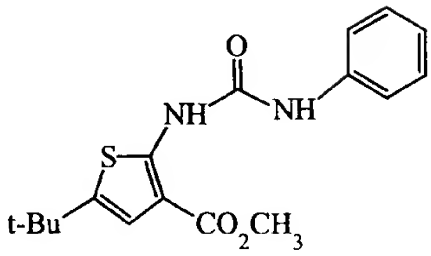
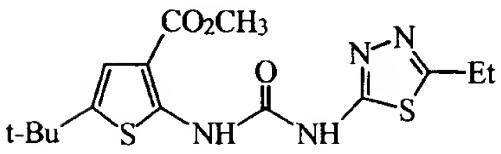
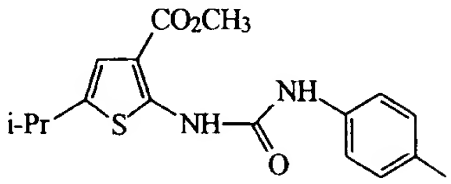


13. A compound according to claim 8, of the formulae









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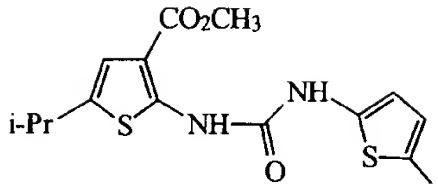
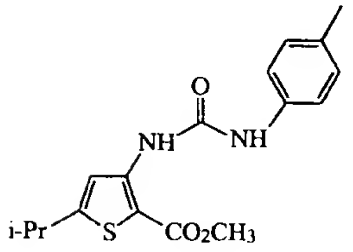
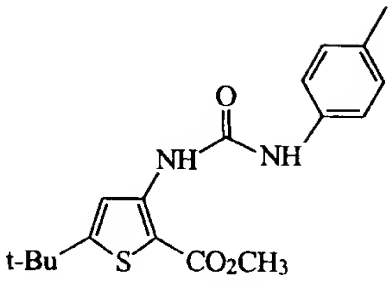
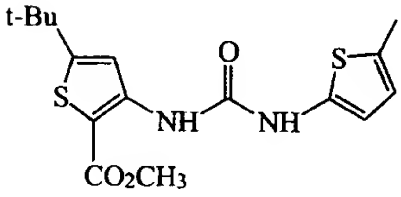
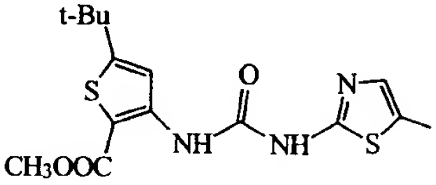


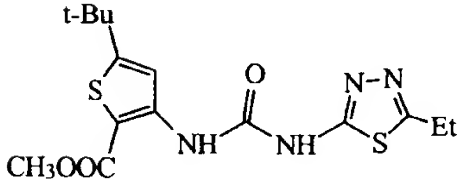
14. A compound according to claim 8, of the formulae

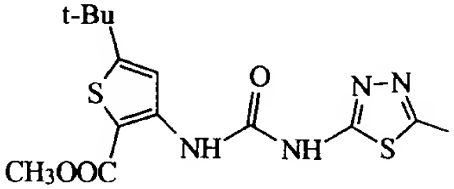


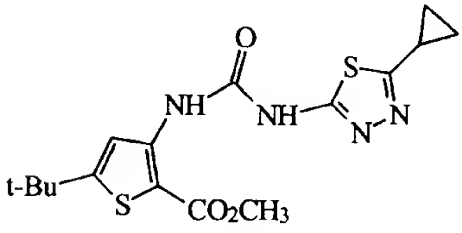


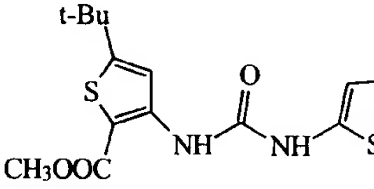


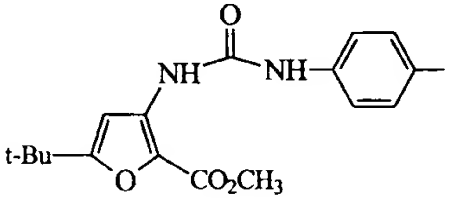


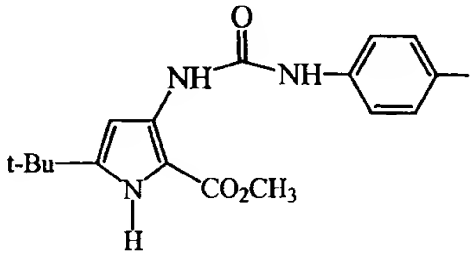


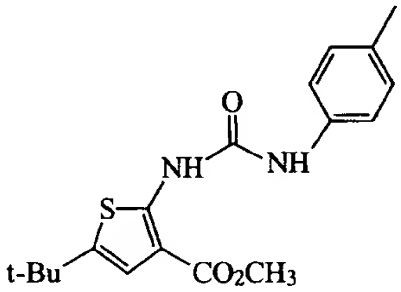












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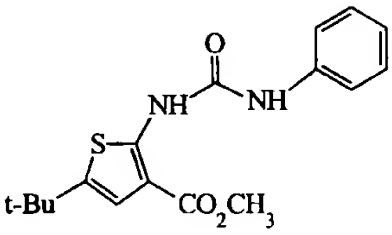

15. A pharmaceutical composition comprising a compound according to claim 8 and a physiologically acceptable carrier.

16. A pharmaceutical composition comprising a compound according to claim 14 and a physiologically acceptable carrier.

17. A pharmaceutical composition comprising a compound according to claim 8 and a physiologically acceptable carrier, in sterile form.